46 Cancer of the Stomach

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INTRODUCTION

Adenocarcinoma of the stomach was the leading cause of cancer-related death worldwide through most of the 20th century. It now ranks second only to lung cancer, and an estimated 870,000 new cases are diagnosed annually, and 650,000 deaths (10% of all cancer deaths) worldwide.[1] In 2011, the epidemiologic data on cancer of the stomach was updated. It now ranks fourth after lung cancer, breast cancer, and colorectal cancer. An estimated 989,600 new cases are diagnosed annually, with 738,000 deaths (10% of all cancer deaths) worldwide.[2] In the West, the incidence of gastric cancer has decreased, potentially because of changes in diet, food preparation, and other environmental factors. The declining incidence has been dramatic in the United States, where this disease ranked sixth as a cause of cancer-related death during the period of 2000 to 2005.[3] It is estimated that in 2009, 21,130 new gastric cancer cases were diagnosed in the United States, with approximately 10,600 deaths.[3] Data was updated for 2014 where an estimated 22,220 new cases will be diagnosed in the United States, with approximately 10,990 deaths.[4] Prognosis remains poor except in a few countries. The explanations for this finding are multifactorial. The lack of defined risk factors, disease-specific symptoms, and the low incidence of gastric cancer has contributed to the late stage at diagnosis seen in most Western countries. In Japan, where gastric cancer is endemic, more patients are diagnosed at an early stage, which is reflected in higher overall survival (OS) rates.

The decline in incidence has been limited to noncardia gastric cancers.[5] The number of newly diagnosed cases of proximal gastric and esophagogastric junction (EGJ) adenocarcinomas has increased six-fold since the mid-1980s.[6] These proximal tumors are thought to be biologically more aggressive and more complex to treat. The only chance of cure is complete surgical resection. However, even after what is believed to be a "curative" gastrectomy, disease recurs in the majority of patients. Efforts to improve these poor results have focused on developing effective pre- and postoperative systemic and regional adjuvant therapies. This chapter details the state-of-the-art regarding the origins, screening, diagnosis, treatment, and palliation of this significant worldwide health problem.

ANATOMIC CONSIDERATIONS

The stomach begins at the gastroesophageal junction and ends at the pylorus (Fig. 46.1). Cancers arising from the proximal greater curvature may directly involve the splenic hilum and tail of pancreas, whereas more distal tumors may invade the transverse colon. Proximal cancers may extend into the diaphragm, spleen, or the left lateral segment of the liver. A recent study reported on the potential benefits and harms of complete resection even when the tumor invades adjacent abdominal visceral structures (pT4b).[7] In this large multicenter cohort series of 2,208 patients who underwent curative intent resection, 206 patients had pT4b tumors and 112 underwent resection of adjacent organs as part of en bloc gastric cancer resection. The overall 5-year survival rate for this group of patients was 27.2%, suggesting that patients do have a chance at long-term survival if their tumor can be removed en bloc with involved adjacent organs, thereby supporting the role of multivisceral resection if required and technically feasible.[7]

The blood supply to the stomach is extensive and is based on vessels arising from the celiac axis (see Fig. 46.1). The right gastric artery arises from the hepatic artery proper (50% to 68%), left hepatic artery (29% to 40%), or from the common hepatic artery (3.2%). The left gastric artery originates from the celiac axis directly (90%) and may arise from the common hepatic artery (2%), splenic artery (4%), or aorta or from the superior mesenteric artery (3%). Both right and left gastric arteries course along the lesser curvature. Along the greater curvature are the right gastroepiploic artery, which originates from the gastroduodenal artery at the inferior border of the proximal duodenum (rarely from the superior mesenteric artery), and the left gastroepiploic artery (highly variable artery), branching from the distal (72%), inferior, middle splenic artery laterally. The short gastric arteries (vasa brevia, five to seven separate vessels) arise directly from the splenic artery or the left gastroepiploic artery. The posterior (dorsal) gastric artery (17% to 68%) may arise from the splenic artery to supply the distal esophagus, cardia, and fundus. The preservation of any of these vessels in the course of a subtotal gastrectomy for carcinoma is not necessary, and the most proximal few centimeters of remaining stomach are well supplied by collateral flow from the lower segmental esophageal arterial arcade. The rich submucosal blood supply of the stomach is an important factor in its ability to heal rapidly and produce a low incidence of anastomotic disruption following radical gastric resection. The venous drainage of the stomach tends to parallel the arterial supply. The venous efflux ultimately passes through the portal venous system, and this is reflected in the fact that the liver is the primary site for distant metastatic spread.

The lymphatic drainage of the stomach is extensive, and distinct anatomic groups of perigastric lymph nodes have been defined according to their relationship to the stomach and its blood supply. There are six perigastric lymph node groups. In the first echelon (stations 1 through 6) are the right and left pericardial nodes (stations 1 and 2). Along the lesser curvature are the lesser curvature nodes (station 3) and the suprapyloric nodes (station 5). Along the greater curvature, the gastroepiploic nodes or greater curvature nodes (station 4), and the subpyloric nodes (station 6). In the second echelon (stations 7 through 12) are the nodes along named arteries, which include the left gastric, common hepatic, celiac, splenic hilum, splenic artery, and hepatoduodenal lymphatics (stations 7 through 12, respectively), which drain into the celiac and periaortic lymphatics. The third echelon (stations 13 through 16) contains the posterior to pancreatic head, superior mesenteric artery, middle colic artery, and para-aortic lymphatics (stations 13 through 16, respectively). Proximally are the lower esophageal lymph nodes; extensive spread of gastric cancer along the intrathoracic lymph channels may be manifested clinically by a metastatic lymph node in the left supraclavicular fossa (Virchow's node) or left axilla (Irish's node). Tumor spread to the lymphatics in the hepatoduodenal ligament can extend along the falciform ligament and result in subcutaneous periumbilical tumor deposits (Sister Mary Joseph's nodes).

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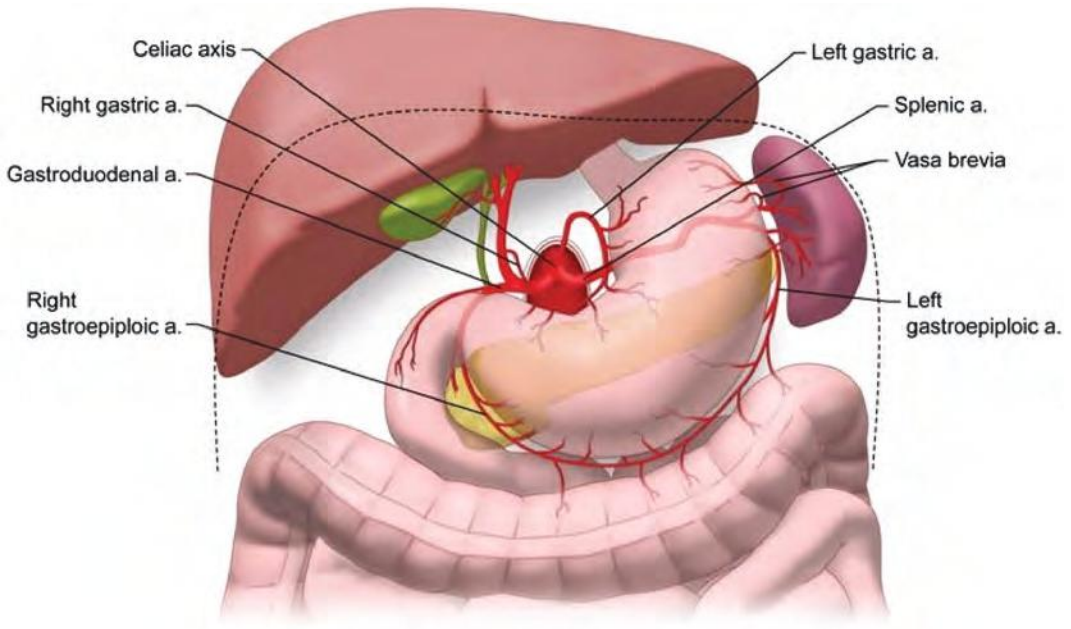

Figure 46.1 Blood supply to the stomach and anatomic relationships of the stomach with other adjacent organs likely to be involved by direct extension of a T4 gastric tumor.

PATHOLOGY AND TUMOR BIOLOGY

Approximately 95% of all gastric cancers are adenocarcinomas. The term *gastric cancer* refers to adenocarcinoma of the stomach. Other malignant tumors are rare and include squamous cell carcinoma, adenoacanthoma, carcinoid tumors, small cell carcinoma, mucinous carcinoma, hepatoid adenocarcinoma, oncocytic (parietal gland) carcinoma, sarcomatoid carcinoma, lymphoepithelioma-like carcinoma, adenocarcinoma with rhabdoid features, gastric carcinoma with osteoclastlike giant cells, neuroendocrine tumor, gastrointestinal stromal tumor, or leiomyosarcoma.[8] Although no normal lymphoid tissue is found in the gastric mucosa, the stomach is the most common site for lymphomas of the gastrointestinal tract. The increased awareness of association between mucosa-associated lymphoid tissue lymphomas and *Helicobacter pylori* may explain, in part, the rise in incidence,[9] although the incidence of mucoas-associated lymphoid tissue gastric lymphomas is decreasing likely because of effective treatment against *H. pylori*.[10]

In terms of pathogenesis, two new concepts are worth mentioning: bone marrow participation in gastric carcinogenesis and gastric cancer stem cells. It has been hypothesized that the gastric epithelial cells acquiring abnormal phenotype (resembling intestinal epithelium) originate from gastric stem cells localized to the only cell replication zone of the gastric glands (i.e., the isthmus). However, Houghton et al.,[11] Stoicov et al.,[12,13] and Li et al.[14] demonstrated in a rodent model of *Helicobacter*-induced gastric cancer that the entire cancer mass was derived from cells originating in the bone marrow. This interesting phenomenon was observed by other authors studying solid cancers in patients receiving bone marrow transplantation.[15] Recent evidence proposes the existence of cancer stem cells or stemlike cancer cells in various cancers. Although controversial, cancer stem cells are defined as cancer cells with the exclusive ability to initiate tumors, metastasize, and self-renew tumors. In gastric cancer, several investigators suggested the existence of gastric cancer stem cells (i.e., CD44+) and side population cells.[16,17] These cells showed relative resistance to chemotherapy and radiation, and exclusive ability to initiate tumors. These important observations might lead to novel approaches to the diagnosis and treatment of gastric cancer in the next decade.

HISTOPATHOLOGY

Several staging schemas have been proposed based on the morphologic features of gastric tumors. The Borrmann classification divides gastric cancer into five types depending on macroscopic appearance. Type I represents polypoid or fungating cancers, type II encompasses ulcerating lesions surrounded by elevated borders, type III represents ulcerated lesions infiltrating the gastric wall, type IV includes diffusely infiltrating tumors, and type V gastric cancers are unclassifiable cancers.[18] The gross morphologic appearance of gastric cancer and the degree of histologic differentiation are not independent prognostic variables. Ming[19] has proposed a histomorphologic staging system that divides gastric cancer into either a prognostically favorable expansive type or a poor prognosis infiltrating type. Based on an analysis of 171 gastric cancers, the expansive-type tumors were uniformly polypoid or superficial on gross appearance, whereas the infiltrative tumors were almost always diffuse. Grossly ulcerated lesions were divided between the expansive or infiltrative forms. Broder's classification of gastric cancer grades tumors histologically from 1 (well-differentiated) to 4 (anaplastic). Bearzi and Ranaldi[20] have correlated the degree of histologic differentiation with the gross appearance of 41 primary gastric cancers seen on endoscopy. Ninety percent of protruding or superficial cancers were well differentiated (Broder's grade 1), whereas almost half of all ulcerated tumors were poorly differentiated or diffusely infiltrating (Broder's grades 3 and 4).

The most widely used classification of gastric cancer is by Laurén.[21] It divides gastric cancers into either intestinal or diffuse forms. This classification scheme, based on tumor histology, characterizes two varieties of gastric adenocarcinomas that manifest distinctively different pathology, epidemiology, genetics, and etiologies. The intestinal variety represents a differentiated cancer with a tendency to form glands similar to other sites in the gastrointestinal tract, but in particular the colon type; hence the intestinal type. In contrast, the diffuse form exhibits very little cell cohesion with a predilection for extensive submucosal spread and early metastases. Although the diffuse-type cancers are associated with a worse outcome than the intestinal type, this finding is not independent of tumor, node, and metastasis (TNM) stage. The molecular pathogenesis of these two distinct forms of gastric cancer is also different. Although the intestinal type represents

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H. pylori–initiated multistep progression with less defined progressive genetic alterations, the diffuse type main carcinogenic event is loss of expression of E-cadherin (*CDH1* gene). E-cadherin is a molecule involved in cell-to-cell adhesion; loss of its expression leads to noncohesive growth, hence the diffuse type. In tumors that display both intestinal and diffuse phenotypes, the *CDH1* mutation and loss of E-cadherin function are observed only within the diffuse phenotype.[22]

PATTERNS OF SPREAD

Carcinomas of the stomach can spread by local extension to involve adjacent structures and can develop lymphatic metastases, peritoneal metastases, and distant metastases. These extensions can occur by the local invasive properties of the tumor, lymphatic spread, or hematogenous dissemination. The initial growth of the tumor occurs by penetration into the gastric wall, extension through the wall, within the wall longitudinally,[23] and subsequent involvement of an increasing percentage of the stomach. The two modes of local extension that can have major therapeutic implications are tumor penetration through the gastric serosa, where the risk of tumor invasion of adjacent structures or peritoneal spread is increased, and lymphatic involvement. Zinninger[24] has evaluated spread within the gastric wall and has found a wide variation in its extent. Tumor spread is often through the intramural lymphatics or in the subserosal layers.[23] Local extension can also occur into the esophagus or the duodenum.[25] Duodenal extension is rare (0.5% to 1.8% of all resected cases),[26] portrays poor prognosis, and is principally through the muscular layer by direct infiltration and through the subserosal lymphatics, but is not generally to any great extent.[27] Extension into the esophagus occurs primarily through the submucosal lymphatics.[28]

Local extension does not occur solely by radial intramural spread but also by deep invasion through the wall to adjacent structures[23] (omentum, spleen, adrenal gland, diaphragm, liver, pancreas, or colon). Many studies report that 60% to 90% of patients had primary tumors penetrating the serosa or invading adjacent organs and that at least 50% had lymphatic metastases. In the largest series reporting on 10,783 patients with gastric cancer from Korea, 57% of the patients had lymph node metastasis, and the average number of involved lymph nodes was five.[29,30] Of the 1,577 primary gastric cancer cases admitted to Memorial Sloan Kettering Cancer Center (MSKCC) between July 1, 1985, and June 30, 1998, 60% of the 1,221 resected cases had evidence of serosal penetration and 68% had positive nodes. Lymph node metastases were found in 18% of pT1 lesions, and 60% of pT2 lesions after R0 resection in 941 patients. The highest incidence of lymphatic metastasis was seen in tumors diffusely involving the entire stomach. Tumors located at the gastroesophageal junction also had a high incidence relative to other sites.[31]

The pattern of nodal metastases also varies depending on the location of the primary site. In a study, reporting on 1,137 patients with early gastric cancer (EGC), tumors located in the upper, middle, and lower third of the stomach had 12%, 10%, and 8% nodal involvement, respectively. The most common nodal station metastases for the upper, middle, and lower third of the stomach were stations 3 (lesser curvature), 3/4/7 (lesser/greater curvature/left gastric artery), and 3/4/6 (lesser/greater curvature/infrapyloric), respectively.[32] Earlier studies that included more advanced gastric cancers showed that the left gastric artery nodes were at increased risk for nodal metastases independent of tumor location.[32,33]

Gastric cancer recurs in multiple sites, locoregionally and systemically. Patterns of failure are variable. These differences are likely related to the patient cohorts evaluated, the time at which failure was determined, and the method of determination of failure patterns. Recent series from the MSKCC and Korea do shed light on modern patterns of failure.[31,34] In the report from MSKCC, recurrence patterns of 1,038 patients who underwent R0 gastrectomy with D2 lymphadenectomy (61%) were analyzed; complete data on recurrence were available in 367 (74%) of 496 patients who experienced recurrence. The locoregional area was involved in 199 (54%) patients. Distant sites were involved in 188 (51%) patients, and peritoneal recurrence was detected in 108 (29%) patients. More than one site of recurrence was detected: distal, peritoneal, and locoregional recurrences in 9 (2.5%); locoregional and peritoneal in 34 (9.3%); locoregional and distant in 61 (16.6%); and distant and peritoneal in 15 (4.1%) patients. On multivariate analysis, peritoneal recurrence was associated with female gender, advanced T stage, and distal and diffuse type tumors; locoregional recurrence was associated with proximal location, early T stage, and intestinal type tumors. In the study from Korea, recurrence patterns were analyzed in 2,038 patients who were treated with potentially curative gastrectomy.[34] Of 508 patients who developed recurrence, 33% involved locoregional sites, 44% were peritoneal, and 38% were distant. At time of presentation, 35% of patients presented with distant metastasis, with 4% to 14% having liver metastases.[35,36]

CLINICAL PRESENTATION AND PRETREATMENT EVALUATION

Signs and Symptoms

Because of the vague, nonspecific symptoms that characterize gastric cancer, many patients are diagnosed with advanced-stage disease. Patients may have a combination of signs and symptoms such as weight loss (22% to 61%)[37]; anorexia (5% to 40%); fatigue, epigastric discomfort, or pain (62% to 91%); and postprandial fullness, heart burn, indigestion, nausea, and vomiting (6% to 40%). None of these unequivocally indicates gastric cancer. In addition, patients may be asymptomatic (4% to 17%).[38] Weight loss and abdominal pain are the most common presenting symptoms at initial encounter.[39–41] Weight loss is a common symptom, and its clinical significance should not be underestimated. Dewys et al.[42] found that in 179 patients with advanced gastric cancer, >80% of patients had a >10% decrease in body weight before diagnosis. Furthermore, patients with weight loss had a significantly shorter survival than did those without weight loss.[40]

In some patients, symptoms may suggest the presence of a lesion at a specific location. Up to 25% of the patients have history/symptoms of peptic ulcer disease.[39] A history of dysphagia or pseudoachalasia may indicate the presence of a tumor in the cardia with extension through the gastroesophageal junction.[43] Early satiety is an infrequent symptom of gastric cancer but is indicative of a diffusely infiltrative tumor that has resulted in loss of distensibility of the gastric wall. Delayed satiety and vomiting may indicate pyloric involvement. Significant gastrointestinal bleeding is uncommon with gastric cancer; however, hematemesis does occur in approximately 10% to 15% of patients, and anemia in 1% to 12% of patients. Signs and symptoms at presentation are often related to spread of disease. Ascites, jaundice, or a palpable mass indicate incurable disease.[40] The transverse colon is a potential site of malignant fistulization and obstruction from a gastric primary tumor. Diffuse peritoneal spread of disease frequently produces other sites of intestinal obstruction. A large ovarian mass (Krukenberg's tumor) or a large peritoneal implant in the pelvis (Blumer's shelf), which can produce symptoms of rectal obstruction, may be palpable on pelvic or rectal examination.[37,44] Nodular metastases in the subcutaneous tissue around the umbilicus (Sister Mary Joseph's node) or in peripheral lymph nodes such as in the supraclavicular area (Virchow's node) or axillary region (Irish's node) represent areas in which a tissue diagnosis can be established with minimal morbidity.[45] There is no symptom complex that occurs early in the evolution of gastric cancer that can identify individuals for further diagnostic measures. However, alarming symptoms (dysphagia,

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weight loss, and palpable abdominal mass) are independently associated with survival; increased number and the specific symptom is associated with mortality.[40,41]

Screening

A list of risk factors associated with gastric cancer is outlined in Table 46.1. These factors might be use for risk stratification in screening programs. Mass screening programs for gastric cancer have been most successful in high-risk areas, especially in Japan.[46] A variety of screening tests have been studied in Japanese patients, with a sensitivity and specificity of approximately 90%.[40] Screening typically includes serology for *H. pylori*, the use of double-contrast barium radiographs, or upper endoscopy with risk stratification (OLGA staging system for gastric cancer risk[46,47]).

Ohata et al.[48] reported on 4,655 asymptomatic patients with an average age of 50 years old who were followed for 7.7 years. Atrophic gastritis was identified using pepsinogen and *H. pylori* testing: 2,341 (52%) were *H. pylori*–positive with nonatrophic gastritis, 967 (21%) were *H. pylori*–negative without atrophic gastritis, 1,316 (28%) were *H. pylori*–positive with atrophic gastritis, and 31 (0.7%) had severe atrophic gastritis. The rates of gastric cancer development per population per year were 107/100,000 for *H. pylori*–positive with nonatrophic gastritis, 0/100,000 for *H. pylori*–negative without atrophic gastritis, 238/100,000 for *H. pylori*–positive with atrophic gastritis, and 871/100,000 for severe atrophic gastritis. Thus the number of endoscopies needed to detect one cancer was 1/1,000, 0/1,000, 1/410, and 1/114, respectively. Similar data were reported on 6,985 patients by Watabe et al.[49] Surveillance in endemic populations is clinically important because EGC has a very high cure rate with surgical treatment. However, the fact that gastric cancer remains one of the top causes of death in Japan indicates the limitations of a mass-screening program when the entire population at risk is not effectively screened. However, more recent studies indicate that for surveillance programs to be effective and feasible from an economical perspective, they should be instituted only in high-risk populations (>20/100,000 incidence of disease) and include the following components: detection and eradication of *H. pylori*, serum pepsinogen (pepsinogen I/II ratio), endoscopy with biopsy, and risk stratification before and after *H. pylori* eradication using a system such as the OLGA staging system for gastric cancer risk. Such programs are expected to avoid long-term repeated screening of approximately 70% of the population who are at low risk of developing gastric cancer.[46,50–52] A US study found that screening and eradication of *H. pylori* in Japanese Americans is cost-effective in preventing gastric cancer.[53] These findings were confirmed by two studies from the United Kingdom.[54,55]

TABLE 46.1

Factors Associated with Increased Risk of Developing Stomach Cancer

Acquired Factors

- Nutritional
  - High salt consumption
  - High nitrate consumption
  - Low dietary vitamin A and C
  - Poor food preparation (smoked, salt cured)
  - Lack of refrigeration
  - Poor drinking water (well water)
- Occupational
  - Rubber workers
  - Coal workers
- Cigarette smoking
- *Helicobacter pylori* infection
- Epstein-Barr virus
- Radiation exposure
- Prior gastric surgery for benign gastric ulcer disease
- Prior treatment for mucosa-associated lymphoid tissue lymphoma

Genetic Factors

- Type A blood
- Pernicious anemia
- Family history without known genetic factors (first-degree relative with gastric cancer)
- Hereditary diffuse gastric cancer (*CDH1* mutation)
- Familial gastric cancer
- Hereditary nonpolyposis colon cancer
- Familial adenomatous polyposis
- Li-Fraumeni syndrome
- *BRCA1* and *BRAC2*
- Precursor lesions
  - Adenomatous gastric polyps
  - Chronic atrophic gastritis
  - Dysplasia
  - Intestinal metaplasia
  - Menetrier disease
- Ethnicity (in the United States, gastric cancer is more common among Asian/Pacific Islanders, Hispanics and African Americans)
- Obesity (the strength of this link is not clear)

PRETREATMENT STAGING

Tumor Markers

Most gastric cancers have at least one elevated tumor marker, but some benign gastric diseases show elevated serum tumor markers as well. Tumor markers in gastric cancer continue to have limited diagnostic usefulness, with their role more informative in follow-up after primary treatment. The most commonly used markers are serum carcinoembryonic antigen (CEA), cancer antigen (CA) 19-9, CA 50, and CA 72-4. There is wide variation in the reported serum levels of these markers; positive CEA and CA 19-9 levels varied from 8% to 58% and 4% to 65%, respectively. Overall, the sensitivity of each serum tumor marker alone as a diagnostic marker of gastric cancer is low. However, when the levels are elevated, it does usually correlate with stage of disease. Combining CEA with other markers, such as CA 19-9, CA 72-4, or CA 50, can increase sensitivity compared with CEA alone.[56–62]

In a large study evaluating serum CEA, α-fetoprotein, human chronic gonadotropin-β, CA 19-9, CA 125, as well as tissue staining for *HER2* in gastric cancer patients, only human chronic gonadotropin-β level >4 IU/L and a CA 125 level ≥350 U/mL had prognostic significance. Elevated serum tumor marker levels in gastric cancer before chemotherapy may reflect not just tumor burden but also biology of disease.

Endoscopy

Endoscopy is the best method to diagnose gastric cancer as it visualizes the gastric mucosa and allows biopsy for a histologic diagnosis. Chromoendoscopy helps identify mucosal abnormalities through topical mucosal stains. Magnification endoscopy is used to magnify standard endoscopic fields by 1.5- to 150-fold. Narrow band imaging affords enhanced visualization of the mucosal microvasculature. Confocal laser endomicroscopy permits in vivo, three-dimensional microscopy including subsurface structures with diagnostic accuracy, sensitivity, and specificity of 97%, 90%, and 99.5%, respectively.[63–65]

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Endoscopic ultrasound (EUS) is a tool for preoperative staging and selection for neoadjuvant therapy. It is used to assess the T and N stage of primary tumors. A study of 225 patients from MSKCC found that the concordance between EUS and pathology was lower than expected. The accuracy for individual T and N stage were 57% and 50%, respectively. However, the combined assessment of N stage and serosal invasion identified 77% of the patients at risk of disease-related death after curative resection.[66] Other investigators compared the accuracy of EUS with that of multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI) and found that the overall accuracy was 65% to 92% (EUS), 77% to 89% (MDCT), and 71% to 83% (MRI) for T stage, and 55% to 66% (EUS), 32% to 77% (MDCT) for N stage, respectively. The corresponding sensitivity and specificity for serosal involvement were 78% to 100% (EUS), 83% to 100% (MDCT), and 89% to 93% (MRI) for T stage, and 68% to 100% (EUS), 80% to 97% (MDCT), and 91% to 100% (MRI) for N stage, respectively.[65,67]

Computed Tomography

Once gastric cancer is suspected, a triphasic CT with oral and intravenous contrast of the abdomen, chest, and pelvis is imperative. In a study of 790 patients who underwent MDCT prior to surgery, the overall accuracy in determining T stage was 74% (T1 46%, T2 53%, T3 86%, and T4 86%), and for N staging it was 75% (N0 76%, N1 69%, and N2 80%). The sensitivity, specificity, and accuracy for lymph node metastasis were 86%, 76%, and 82%, respectively.[68] MDCT with thin-sliced multiplanar reconstruction (MPR) and water filling is increasingly used. The accuracy rate for advanced gastric cancer was 96% and for EGC it was 41%. An improvement on axial CT and MPR-MDCT was the addition of staging with three-dimensional MPR-MDCT. The detection rate for MPR with virtual gastroscopy was 98%. MPR-MDCT with combined water and air distention is superior to conventional axial imaging.[69]

Magnetic Resonance Imaging

MRI is not used routinely in preoperative staging of gastric cancer. Several studies have demonstrated that CT and MRI are comparable in terms of accuracy and understaging.[70,71] However, MRI is a useful modality to further characterize liver lesions identified on preoperative CT staging workup.

Positron Emission Tomography

Whole-body 2-[18F]-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) is being applied increasingly in the evaluation of gastrointestinal malignancies. In gastric cancer, approximately half of the primary tumors are FDG-negative; the diffuse (signet cell) subtype was most likely to be non-FDG avid, likely because of decreased expression of the glucose transporter-1 (Glut-1).[72] In patients with non-FDG–avid primary tumor, FDG-PET/CT is not useful.[72–76] PET/CT was tested as a tool to predict response to neoadjuvant chemotherapy. Ott et al.[77] reported 90% 2-year survival in patients with PET-defined response (<35% decrease standardized uptake value [SUV]) versus 25% for patients not responding to PET. PET response could be detected as early as 14 days. At least 60% of the patients were PET-nonresponding patients and thus could have been spared further chemotherapy. Authors of the MUNICON trial reported on patients who were PET nonresponders by day 14 after cisplatin and fluorouracil (5-FU) (CF) neoadjuvant chemotherapy, and subsequently were sent for surgery, and patients who were PET responders and continued 3 months of neoadjuvant therapy before surgery. The PET-responding patients had a survival benefit (hazard ratio [HR] = 2.13; p <0.15). In PET-nonresponding patients, stopping the chemotherapy did not affect long-term survival.[78] Recent studies, including one large meta-analysis, showed that in terms of diagnostic accuracy and lymph node staging EUS, MDCT, MRI, and PET/CT are comparable modalities. There were no significant differences between mean sensitivities and specificities.[79,80] Even in patients whose tumors were FDG-avid, FDG-PET/CT scans did not identify occult peritoneal disease (0 of 18), but did identify extraperitoneal M1 disease in nine patients with bone (n = 2), liver (n = 4), and retroperitoneal lymph node (n = 3) involvement. In patients with FDG-avid tumors, PET may be useful in detecting metastatic disease and follow-up for recurrence. Interestingly, the presence of Glut-1– and FDG-avid gastric cancers may be associated with decreased OS.[72] The role of PET/CT in the primary staging of gastric cancer remains to be established; its role might be better defined in advanced disease.

In a prospective study of 113 patients who were clinically staged as locally advanced but nonmetastatic gastric cancer (T3-T4, Nx or N+, M0), investigators found that FDG-PET/CT did identify occult metastatic disease in about 10% of patients. In this study, FDG-PET/CT did not identify occult peritoneal disease, suggesting a necessary role for laparoscopy in preoperative staging of locally advanced gastric cancer. A cost evaluation was also performed, and it suggested that if FDG-PET/CT is included as part of the staging algorithm, that would result in an estimated cost savings of approximately $13,000 US dollars per patient.[81]

Staging Laparoscopy and Peritoneal Cytology

Staging laparoscopy with peritoneal lavage should be an integral part of the pretreatment staging evaluation of patients believed to have localized gastric cancer. Current noninvasive modalities used in preoperative staging of gastric cancer have sensitivities significantly lower than 100%, particularly in cases of low-volume peritoneal carcinomatosis.[82–84] Current CT techniques cannot consistently identify low-volume macroscopic metastases that are ≤5 mm in size. Laparoscopy directly inspects the peritoneal and visceral surfaces for detection of CT-occult, small-volume metastases. Staging laparoscopy also allows for assessment of peritoneal cytology and laparoscopic ultrasound. Laparoscopic staging is done to spare nontherapeutic operations and for potential stratification in various trials.[85]

The rate of detection of CT-occult M1 disease by laparoscopy depends on the quality of CT scanning and interpretation.[86] Muntean et al.[87] reported on 98 patients with primary gastric cancer: 45 underwent staging laparoscopy with subsequent surgery and 53 went directly to surgery. An unnecessary laparotomy was avoided in 38% of the patients. The overall sensitivity and specificity were 89% and 100%, respectively. Nonetheless, even high-quality MDCT is insufficiently sensitive for detection of low-volume extragastric disease and thus CT, EUS, and laparoscopy are complementary staging studies.[88,89]

The value of peritoneal cytology as a preoperative staging tool in patients with gastric cancer who are potential candidates for curative resection by EUS and CT has been examined by several investigators. Bentrem et al.[90] reported on 371 patients who underwent R0 resection, 6.5% of whom had positive cytology after staging laparoscopy. Median survival of patients with positive cytology was 14.8 versus 98.5 months for patients with negative cytology findings (p <0.001). Positive cytology predicted death from gastric cancer (relative risk = 2.7; p <0.001) and is tantamount to M1 disease. Several groups confirmed these findings and concluded that staging laparoscopy with peritoneal cytology can change the management of gastric cancer in 6.5% to 52% of patients.[85,91–94]

Laparoscopy can be performed as a separate staging procedure prior to definitive treatment planning or immediately prior to planned laparotomy for gastrectomy. When performed as a separate procedure, laparoscopy has the disadvantage of the additional risks and expense of a second general anesthetic. However,

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separate procedure laparoscopy allows the additional staging information including cytology acquired at laparoscopy to be reviewed and discussed with the patient and in multidisciplinary treatment group prior to definitive treatment planning. Laparoscopic ultrasound (LUS) and "extended laparoscopy" are techniques that may increase the diagnostic yield of laparoscopy. Preliminary results reveal conflicting data on the added benefit of LUS and extended laparoscopy.[95–97] Further prospective studies will be required to evaluate the cost-benefit relationship of LUS and extended laparoscopy in the routine or selective workup of patients with gastric cancer.

Although laparoscopic staging is thought to detect CT-occult metastatic disease in approximately 40% of patients and spares nontherapeutic operations in approximately one-third of patients with gastric cancer, one needs to remember that tumor biology, not staging, will eventually guide outcomes. Clearly, not all patients benefit from preoperative laparoscopic staging; therefore, future studies should address the issue of selective laparoscopy based on noninvasive staging (i.e., patients with T1 tumors). Staging laparoscopy with or without cytology should be considered only if therapy will be altered consequent to information obtained by laparoscopy.[82]

STAGING, CLASSIFICATION, AND PROGNOSIS

For patients with surgically treated gastric adenocarcinoma, both pathologic staging (American Joint Committee on Cancer [AJCC]/International Union Against Cancer [UICC] or Japanese system) and classification of the completeness of resection (R classification) should be done. Although not formal components of the stage grouping, the AJCC recommends collection of additional prognostic factors: tumor location, serum CEA and CA 19.9, and histopathologic grade and type.[98]

American Joint Committee on Cancer/International Union Against Cancer Tumor, Node, Metastasis Staging

The AJCC/UICC TNM staging system for gastric cancer is outlined in Table 46.2.[98] The AJCC/UICC stage-stratified survival rates of 10,601 patients treated by surgical resection from the Surveillance, Epidemiology, and End Results program 1973 to 2005 public-use file diagnosed in years 1991 to 2000 are shown in Fig. 46.2. Several definitions in the most recent version of the AJCC (2010) differ from the previous version (2002). Tumors arising at the EGJ including Siewert type I or arising in the stomach ≤5 cm from the EGJ and crossing into the EJG including Siewert types II and III are staged using the TNM system for esophageal adenocarcinoma. Gastric tumors lying ≤5 cm from the EGJ but that do not cross the EGJ into the esophagus are staged as gastric cancer.[98]

In the AJCC/UICC staging system, tumor (T) stage is determined by depth of tumor invasion into the gastric wall and extension into adjacent structures (Fig. 46.3). The relationship between T stage, the overall stage, and survival is well defined (see Fig. 46.2). Nodal stage (N) is based on the number of involved lymph nodes, a criterion that may predict outcome more accurately than the location of involved lymph nodes.[99,100] Tumors with 1 to 2 involved nodes are classified as pN1, 3 to 6 involved nodes are classified as pN2, and those with 7 or more involved nodes are classified as pN3 (N3a has 7 to 15 nodes and N3b has ≥16 nodes). The use of numerical thresholds for nodal classification has gained increasing acceptance, although the extent of lymphadenectomy and rigor of pathologic assessment may affect results.[101,102] The nodal numerical threshold approach is based on observations that

TABLE 46.2

American Joint Committee on Cancer Staging of Gastric Cancer 2010: Definition of Tumor, Nodes, Metastasis

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures
T4a	Tumor invades serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures
Regional Lymph Nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 2 regional lymph nodes
N2	Metastasis in 3 to 6 regional lymph nodes
N3	Metastases in more than 7 regional lymph nodes
N3a	Metastasis in 7–15 regional nodes
N3b	Metastasis in 16 or more regional nodes
Distant Metastasis (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping			
O	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
	T1	N1	M0
IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
IIIB	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
IIIC	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
IV	Any T	Any N	M1

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com, page 123.

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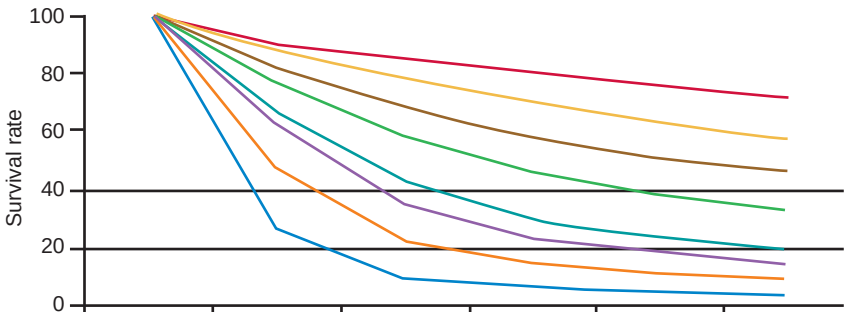

	At Dx	1	2	3	4	5
IA	100.0	90.2	84.4	79.8	74.8	70.8
IB	100.0	87.4	77.9	69.9	62.7	57.4
IIA	100.0	82.1	67.4	57.2	50.2	45.5
IIB	100.0	76.8	58.3	48.0	38.4	32.8
IIIA	100.0	66.5	42.4	29.9	23.5	19.8
IIIB	100.0	61.6	35.4	22.9	17.8	14.0
IIIC	100.0	47.4	21.8	14.2	11.0	9.2
IV	100.0	27.0	10.0	5.6	4.5	4.0

Figure 46.2 Disease-specific survival by American Joint Committee on Cancer stage grouping. *Numbers* beneath x-axis indicate patients at risk. (From Crew KD, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol* 2006;12:354, with permission.)

survival decreases as the number of metastatic lymph nodes increases,[103,104] and that survival significantly decreases at three or more involved[103] lymph nodes and again at seven or more involved lymph nodes.[30,105]

Given the reliance on numerical thresholds for nodal staging, it is extremely important that adequate number of lymph nodes are retrieved surgically and examined pathologically. However, recent reports document poor compliance with AJCC staging primarily because the number of lymph nodes removed and/or examined (≤15) was insufficient.[104,106] Positive peritoneal cytology is classified as M1. Ratio-based lymph node classification (number of positive nodes over number of total nodes resected and evaluated) is an alternative to the threshold-based system currently utilized by the AJCC/UICC staging systems. It may minimize the confounding effects of regional variations in the extent of lymphadenectomy and pathologic evaluation on lymph node staging and thereby

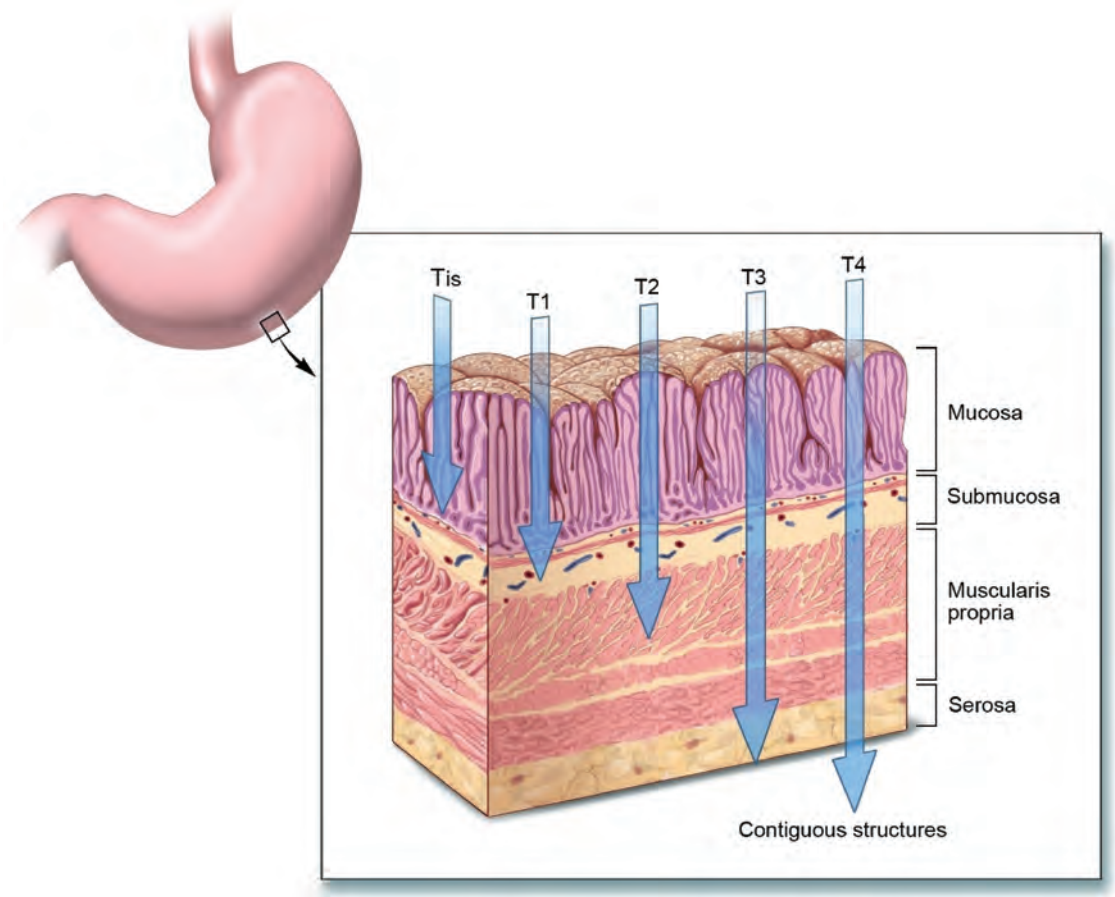

Figure 46.3 Definition of American Joint Committee on Cancer/International Union Against Cancer T stage based on depth of penetration of the gastric wall.

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reduce stage migration.[107–109] Sun et al.[108] evaluated the ratio between metastatic and examined lymph nodes (RML) in a group of 2,159 patients who underwent curative gastrectomy. The anatomic location, number of positive lymph nodes (AJCC/UICC), and RML were analyzed for staging accuracy and relationship to survival. RML was an independent prognostic factor for survival and reduced stage migration. These findings were confirmed by several investigators reporting on approximately 2,000 patients treated by R0 gastrectomy.[107,109–112]

Japanese Staging System

The most recent *Japanese Classification for Gastric Carcinoma* was published in 1998.[113–116] The Japanese classification and staging system is more detailed than the AJCC/UICC staging system and places more emphasis on the distinction between clinical, surgical, pathologic, and "final" staging (prefixes "c," "s," "p," and "f," respectively). For example, a surgically treated and staged patient with locally advanced, nonmetastatic gastric cancer might be staged as pT3, pN2, sH0, sM0, stage f-IIIB (where H0 denotes no hepatic metastases and the "f" prefix denotes final clinicopathologic stage). The Japanese classification system also includes a classification system for EGC (Fig. 46.4).

In the combined superficial types, the type occupying the largest area should be described first, followed by the next type (e.g., IIc + III). Type 0I and type 0IIa are distinguished as follows: type 0I, the lesion has a thickness of more than twice that of the normal mucosa; type 0IIa, the lesion has a thickness up to twice that of the normal mucosa.

Similar to the AJCC/UICC staging system, primary tumor (T) stage in the Japanese system is based on the depth of invasion and extension to adjacent structures, as outlined in Table 46.3.[117] However, the assignment of lymph node (N) stage involves much more rigorous pathologic assessment than is required for AJCC/UICC staging. The Japanese system extensively classifies 18 lymph node regions into four N categories (N0 to N3) depending on their relationship to the primary tumor and anatomic location.[118] Most perigastric lymph nodes (nodal stations 1 through 6) are considered group N1. Lymph nodes situated along the proximal left gastric artery (station 7), common hepatic artery (station 8), celiac axis (station 9), splenic artery (station 11), and proper hepatic artery (station 12) are defined as group N2. Para-aortic lymph nodes (station 16) are defined as group N3. However, some lymph nodes, even perigastric nodes for specific tumor locations, can be regarded as M1 disease (i.e., involvement of station 2 in the case of antral tumors). This is because their involvement in antral tumors is rare and portrays a poor prognosis.[117]

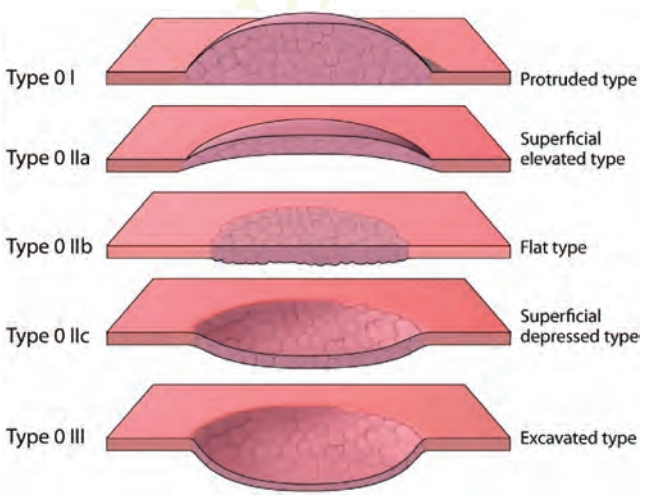

Figure 46.4 Japanese classification system for early gastric cancer.

TABLE 46.3

Japanese Gastric Cancer Association Staging System

Tumor Stage	
T1	Tumor invasion of mucosa and/or muscularis mucosa or submucosa
T2	Tumor invasion of muscularis propria or subserosa
T3	Tumor penetration of serosal
T4	Tumor invasion of adjacent structures
TX	Unknown
Nodal Stage	
N0	No evidence of lymph node metastasis
N1	Metastasis to group 1 lymph nodes, but no metastasis to groups 2 to 3 lymph nodes
N2	Metastasis to group 2 lymph nodes, but no metastasis to group 3 lymph nodes
N3	Metastasis to group 3 lymph nodes
NX	Unknown
Hepatic Metastasis Stage (H)	
H0	No liver metastasis
H1	Liver metastasis
HX	Unknown
Peritoneal Metastasis Stage (P)	
P0	No peritoneal metastasis
P1	Peritoneal metastasis
PX	Unknown
Peritoneal Cytology Stage (CY)	
CY0	Benign/indeterminate cells on peritoneal cytology[a]
CY1	Cancer cells on peritoneal cytology
CYX	Peritoneal cytology was not performed
Other Distant Metastasis (M)	
M0	No other distant metastases (although peritoneal, liver, or cytologic metastases may be present)
M1	Distant metastases other than the peritoneal, liver, or cytologic metastases
MX	Unknown

Stage Grouping

	N0	N1	N2	N3
T1	IA	IB	II	
T2	IB	II	IIIA	
T3	II	IIIA	IIIB	IV
T4	IIIA	IIIB		
H1, P1, CY1, M1				

[a] Cytology believed to be "suspicious for malignancy" should be classified as CY0.
Adapted from Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma - 2nd English Edition. *Gastric Cancer* 1998;1:10.

The Japanese staging system also includes elements not included in the AJCC/UICC system (see Table 46.3). These are macroscopic descriptions of the tumor (EGC subtype or Bormann type for more advanced tumors), extent of peritoneal metastases (classified as P0-1), extent of hepatic metastases (H0-1), and peritoneal cytology findings (CY0-1). Recent comparison of the

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Japanese and AJCC/UICC staging systems in 731 patients suggests that both are comparable.[119] However, older studies suggest that the AJCC/UICC system more accurately estimates prognosis.[101]

Classification of Esophagogastric Junction Cancers

EGJ cancers (i.e., tumors with a definitive component involving the EGJ) are no longer classified by the AJCC as gastric cancers per se. They are briefly reviewed here for historical reasons. Siewert and Stein[120] classified adenocarcinomas of the EGJ (Siewert classification) into three distinct clinical entities that arise within 5 cm of the EGJ: type I arises in the distal esophagus and may infiltrate the EGJ from above, type II arises in the cardia or the EGJ, and type III arises in the subcardial stomach and may infiltrate the EGJ from below. The assignment of tumors to one of these subtypes is based on morphology and the anatomic location of the epicenter of the tumor. The Siewert classification has important therapeutic implications.[121] The lymphatic drainage routes differ for type I versus types II and III lesions. The lymphatic pathways from the lower esophagus pass both cephalad and caudad. In contrast, the lymphatic drainage from the cardia and subcardial regions is caudad. Thus, the Siewert classification provides a practical means for choosing among surgical options. For type I tumors, esophagectomy is required, whereas types II and III tumors can be treated by transabdominal gastrectomy.[121,122]

Resection Classification

The R classification system indicates the amount of residual disease left after tumor resection.[123] R0 indicates no gross or microscopic residual disease, R1 indicates microscopic residual disease (positive margins), and R2 signifies gross residual disease. The R classification has implications for individual patient care and clinical research. Results of clinical trials that include surgery should include information on R status. Readers should be aware of the dual use of the "R" terminology in the gastric cancer literature. Prior to 1995, the Japanese staging and treatment vernacular included an "R level," which described the extent of lymphadenectomy. The latter is now classified by "D" (for dissection) level.

GASTRIC CANCER NOMOGRAMS: PREDICTING INDIVIDUAL PATIENT PROGNOSIS AFTER POTENTIALLY CURATIVE RESECTION

Kattan et al.[103] have developed a nomogram for predicting individual patient 5-year disease-specific survival using established prognostic factors derived from a population of 1,039 patients with gastric cancer treated by R0 surgical resection without neoadjuvant therapy at a single institution (nomograms@mskcc.org). Clinicopathologic factors incorporated in the nomogram include age and gender, primary tumor site, Laurén classification, numbers of positive and negative lymph nodes resected, and depth of invasion. This nomogram was subsequently validated by several authors. Peeters et al.[124] found that the nomogram prognosticates better then the AJCC staging system. Novotny et al.[125] validated the nomogram in 862 patients from Germany and the Netherlands; Strong et al.[126] compared outcomes using the nomogram in 711 patients from the United States and 1,646 patients from Korea. This tool may be useful for individual patient counseling regarding the use of adjuvant therapy, follow-up scheduling, and clinical trial eligibility assessment, and is available for personal handheld computer devices at www.nomograms.org.

Recently, a large retrospective cohort study of 1,273 patients who underwent resection revealed that having a positive family history of gastric cancer (defined as a self-reported history of cancer in first-degree relatives) was associated with significant reduction in disease-free survival (DFS; $p = 0.012$), relapse-free survival ($p = 0.006$), and OS ($p = 0.005$) when compared with those who did not have a family history of gastric cancer. The improvement in outcomes was more pronounced among patients with stage III or IV gastric cancer, with significant adjusted HRs for DFS (HR = 0.49; 95% confidence interval [CI] = 0.29 to 0.84), relapse-free survival (HR = 0.47; 95% CI = 0.30 to 0.87), and OS (HR = 0.47; 95% CI = 0.26 to 0.84), respectively.[127]

TREATMENT OF LOCALIZED DISEASE

Stage I Disease (Early Gastric Cancer)

Classification of Early Gastric Cancer and Risk for Nodal Metastases

The Japanese Research Society for Gastric Cancer has classified EGCs based on endoscopic criteria first established for the description of T1 tumors. The current classification system is used for both in situ and invasive tumors and categorizes tumors based on endoscopic findings as follows: protruded, type 0I; superficial elevated, type 0IIa; flat, type 0IIb; superficial depressed, type 0IIc; and excavated, type 0III (see Fig. 46.4). The English language version of the Japanese EGC classification contains excellent color photos of these subtypes.[128] This classification system is important in describing patients treated by newer gastric-sparing approaches for EGC, such as endoscopic mucosal resection (EMR).[114–116,129] The risk for lymph node metastasis is important when evaluating treatment options for patients with EGC. The frequency and anatomic distribution of nodal disease are related to the depth of tumor invasion. In a Japanese series of >5,000 patients who underwent gastrectomy with lymph node dissection for EGC, none of the 1,230 patients with well-differentiated intramucosal tumors <3 cm in diameter (regardless of ulceration) had lymph node metastases.[130] None of the 929 patients with EGC without ulceration had nodal metastases, irrespective of tumor size. In contrast, in the subset of >2,000 patients with tumors that invaded the submucosa, the frequencies of lymph node involvement for tumors ≤1.0 cm, 1.1 to 2.0 cm, 2.1 to 3.0 cm, and >3.0 cm were 7.9%, 13.3%, 15.6%, and 23.3%, respectively. Thus, once tumors penetrate into the submucosa, the risk for nodal metastasis increases with tumor size.[131–137] The estimates of the frequency of nodal disease in EGC are based on conventional light-microscopic histologic assessment. However, the use of more sensitive techniques such as serial sectioning of individual lymph nodes, immunohistochemistry, or reverse transcriptase-polymerase chain reaction may increase the frequency of detection of occult micrometastatic disease.[138] The clinical significance of micrometastasis remains unknown.

Endoscopic Mucosal Resection

A subset of patients with EGC can undergo an R0 resection without lymphadenectomy or gastrectomy. The Japanese have popularized EMR for EGC. This approach involves the submucosal injection of fluid to elevate the lesion and facilitate complete mucosal resection under endoscopic guidance. Most centers reporting significant experience with EMR are in Japan. There is less experience with EMR in Western countries. Only patients with tumors that have extremely low metastatic potential should be offered EMR. These are generally well-differentiated, superficial type IIa or IIc lesions, <3 cm in diameter, and located in an easily manipulated area. Tumors invading the submucosa are at increased risk for metastasizing to lymph nodes and are not usually considered candidates for EMR.

Recently, Bennett et al.[139] reviewed the available data reporting on EMR for EGC. No randomized controlled trial (RCT) reported

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on EMR. The indications for EMR are well-differentiated lesions, size ≤20 mm in elevated type, ≤10 mm in depressed type, no ulceration, and limited to the mucosa.[140] The incidence of lymph node metastases for such lesions is approximately 1%. Complete resection of selected EGCs can be accomplished in a majority of cases (73.4% to 98%).[139,141,142]

Two retrospective reports indicated that EMR can reduce the risk of local residual tumor, and repeat EMR is an effective option.[143,144] Recurrence after EMR varies with type of EGC. Ida et al.[145] reported on 412 patients: 8 of 199 (4.0%) had recurrence of lesions size 20 to 40 mm; 5 patients were retreated by EMR and 3 underwent open surgery; and none had lymph node metastases. Patients (0/305) with lesions ≤20 mm did not have recurrence. Complication rates associated with EMR are low. Bleeding and perforation are reported in 0% to 20.5% and 0% to 5.2 % of patients, respectively.[141,146–149] The reported morbidity and mortality rates in patients undergoing open surgery ($n = 256$) versus EMR ($n = 56$) were 0.8% and 7.8% versus 0% and 16%, repsectively.[139,150]

Fukase et al.[151,152] reported on the long-term outcomes of patients undergoing open surgery ($n = 116$) versus EMR ($n = 59$). For patients age 65 year or under, the 5- and 10-year survival rates were 100% and 91.7% versus 92.8% and 92.8%, with open surgery and EMR, respectively. For patients older than 65 years of age, the 5- and 10-year survival rates were 100% and 75% versus 80.8% and 80.8%, respectively. The differences were not statistically significant. Similar results were reported by Park et al.[153] and Kim et al.[154]

There are emerging variations of EMR techniques, including the cap suction and cut versus a ligating device. As outcome studies accumulate demonstrating favorable survival, EMR is emerging as the definitive management of selected EGCs and is not just reserved for patients in whom gastrectomy cannot be considered. However, RCTs are needed to establish an outcome advantage over open surgery.[140,155–165]

Limited Surgical Resection

Given the low rate of nodal involvement for patients with EGC, limited resection may be a reasonable alternative to gastrectomy for some patients. There are no well-accepted pretreatment criteria for selection of patients for limited resection. Based on available pathology studies, patients with small (<3 cm) intramucosal tumors and those with nonulcerated intramucosal tumors of any size may be candidates for EMR or limited resection. Surgical options for these patients may include gastrotomy with local excision. This procedure should be performed with full-thickness mural excision (to allow accurate pathologic assessment of T status) and is often aided by intraoperative gastroscopy for tumor localization. Formal lymph node dissection is not required in these patients.

Gastrectomy

Gastrectomy with lymph node dissection should be considered for patients with EGC who cannot be treated with EMR or limited surgical resection, and/or patients who have intramucosal tumors with poor histologic differentiation, or size >3 cm, or who have tumor penetration into the submucosa or beyond. Gastrectomy with lymph node dissection allows for adequate pathologic staging and local therapy for these patients at increased risk of nodal metastasis. Dissection of level I lymph nodes is a reasonable minimum standard at this time for higher risk EGCs. The roles for nodal "sampling" without formal node dissection (D0 dissection) and sentinel lymph node (SLN) mapping and biopsy in the treatment of EGC remain undefined at this time.

Stage II and Stage III Disease

Surgery

Surgical resection of the primary tumor and regional lymph nodes is the cornerstone of treatment for patients with localized gastric cancer. However, for stage II and III disease, surgery is necessary but often not sufficient for cure. The general therapeutic goal is to achieve a microscopically complete resection (R0). A complete discussion of all the technical details of gastric resection and reconstruction is beyond the scope of this chapter. However, specific surgical issues of oncologic significance are addressed here, including the extent of gastrectomy, extent of regional lymph node dissection, and role of partial pancreatectomy and splenectomy. Additional technical details can be found in surgical atlases and the section "Technical Treatment-Related Issues."

Extent of Resection for Mid- and Distal Gastric Cancers. The extent of gastrectomy required for satisfactory primary tumor treatment depends primarily on the gross and microscopic status of surgical margins. For most clinical situations, a 5-cm grossly negative margin around the tumor and microscopically negative surgical margin (R0) are the treatment goals. When gastrectomy is performed with curative intent, frozen-section assessment of proximal and distal resection margins should be used intraoperatively to improve the likelihood that an R0 resection has been attained. Three relatively small prospective RCTs have compared total gastrectomy with partial (subtotal) gastrectomy for distal gastric cancer.[166–168] Overall morbidity, mortality, and oncologic outcome were comparable in each of these RCTs. When the general oncologic goal of an R0 resection can be achieved by a gastric-preserving approach, partial gastrectomy is preferred over total gastrectomy. This is particularly relevant for distal gastric cancers, for which a gastric-preserving R0 approach may minimize the risks of specific sequelae of total gastrectomy such as early satiety, weight loss, and the need for vitamin B_{12} supplementation.

Extent of Resection for Proximal Gastric Cancer. There are many choices for surgical management of adenocarcinomas arising at the EGJ or in the proximal stomach (Siewert types II and III). Many abdominal surgeons have advocated transabdominal approaches with resection of the lower esophagus and proximal stomach or total gastrectomy. Surgeons trained in thoracic surgery have frequently advocated a combined abdominal and thoracic procedure (often termed *esophagogastrectomy*) with an intrathoracic or cervical anastomosis between the proximal esophagus and the distal stomach, or a procedure termed *transhiatal (or blunt) esophagectomy* (THE), which involves resection of the esophagus and EGJ with mediastinal dissection performed in a blunt fashion through the esophageal hiatus of the diaphragm. When THE is performed for adenocarcinoma of the EGJ, gastrointestinal continuity is restored by low cervical anastomosis of the stomach (usually advanced through the esophageal bed in the posterior mediastinum) to the cervical esophagus. Selection among the options has been dependent primarily on individual surgeon training and experience.

The optimal surgical procedure for patients with localized tumors of the EGJ and proximal stomach is a matter of considerable debate. A recently completed Dutch RCT compared transthoracic esophagogastrectomy (TTEG, with abdominal and thoracic incisions) with THE in 220 patients with adenocarcinoma of the esophagus and EGJ.[169] Although this trial was designed for patients with esophageal cancer, 40 (18%) of the patients had adenocarcinomas of the EGJ (Siewert type II), and the operations evaluated are among those considered for patients with Siewert type II or III cancers. Perioperative morbidity was higher after THE, but there was no significant difference in in-hospital mortality compared with TTEG. Although median overall, disease-free, and quality-adjusted survival did not differ significantly between the groups, there was a trend toward improved OS at 5 years with TTEG. These results are judged equivocal, and there is currently no consensus on the optimal surgical approach for patients with Siewert type II tumors.[170] Until longer follow-up of the Dutch trial is available and/or additional RCTs are performed, the surgical approach to these patients will continue to be individualized and determined

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by a constellation of factors including surgeon factors (training and experience), patient factors (age, comorbid conditions, and functional status), and tumor factors (pretreatment T and N stage).

Extent of Lymphadenectomy. There has been intense debate surrounding the extent of lymphadenectomy. It involves at least two important issues: (1) adequate staging in terms of the number of lymph nodes resected surgically and examined pathologically, and (2) adequate therapy (i.e., do some forms of lymphadenectomy result in better outcomes?).[171–182]

Single-institution reports suggest that the number of pathologically positive lymph nodes is of prognostic significance,[100,102,180,183–185] and that removal and pathologic analysis of at least 15 lymph nodes is required for adequate pathologic staging.[99,186] Indeed, the current AJCC staging system accounts for these issues and therefore requires analysis of ≥16 lymph nodes to assign a pathologic N stage.[187] The possible therapeutic benefit of extended lymph node dissection D2 versus D1 dissection has been the focus of six RCTs, which are summarized in Table 46.4.[167,188–193] These trials were performed because retrospective and prospective nonrandomized evidence suggested that extended lymph node dissection may be associated with improved long-term survival.[194] The RCTs tested the hypothesis that removal of additional pathologically positive lymph nodes (not generally removed as part of a standard lymph node dissection) improves survival. The larger RCTs attempted to follow what are referred to as the "Japanese rules" for lymph node classification and dissection that govern the extent of nodal dissection required based on anatomic location of the primary tumor.[195] Using these Japanese definitions, the RCTs compared limited lymphadenectomy of the perigastric lymph nodes (D1 dissection) to en bloc removal of second-echelon lymph nodes (D2 dissection). At least two of the completed trials are underpowered for their primary end point, OS.[167,188] The trials from the Medical Research Council (MRC) of the United Kingdom[189] and the Dutch Gastric Cancer Group[190] have received the most attention and discussion.

The MRC trial registered 737 patients with gastric adenocarcinoma; 337 (46%) patients were ineligible by staging laparotomy because of advanced disease, and 400 (54%) patients were randomized at the time of laparotomy to undergo D1 (200) or D2 (200) lymph node dissection. Postoperative morbidity was significantly greater in the D2 group (46% versus 28%; $p < 0.001$), and in-hospital mortality rates were also significantly higher in the D2 group than in the D1 group (13% versus 6%, $p < 0.04$).[189] The most frequent postoperative complications were related to anastomotic leakage (D2 26% versus D1 11%), cardiac complications (8% versus 2%), and respiratory complications (8% versus 5%). The excess morbidity and mortality seen in the D2 group were thought to be related to the routine use of distal (left) pancreatectomy and splenectomy. Partial pancreatectomy and splenectomy were performed to maximize clearance of lymph nodes at the splenic hilum, primarily for patients with proximal tumors; however, many surgeons now believe that adequate lymph node dissection can be performed with pancreas- and spleen-preserving techniques. Long-term follow-up analysis of patients in the MRC trial demonstrated comparable 5-year OS rates of 35% and 33% in the D1 and D2 dissection groups, respectively. Survival based on death from gastric cancer as the event was also similar in the D1 and D2 groups (HR = 1.05; 95% CI = 0.79 to 1.39), as was recurrence-free survival (HR = 1.03; 95% CI = 0.82 to 1.29). The authors concluded that classic Japanese-style D2 lymphadenectomy (with partial pancreatectomy and splenectomy) offered no survival advantage over D1 lymphadenectomy.

The Dutch Gastric Cancer Group conducted a larger RCT with optimal surgical quality control comparing D1 to D2 lymph node dissection for patients with gastric adenocarcinoma that was updated in 2010 after 15-year follow-up.[196] Between 1989 and July 1993, 1,078 patients were entered, of whom 996 patients were eligible; 711 patients were randomized to D1 dissection ($n = 380$) or D2 dissection ($n = 331$). To maximize surgical quality control, all operations were monitored.[197] Initially, this oversight was done by a Japanese surgeon who trained a group of Dutch surgeons, who in turn acted as supervisors during surgery at 80 participating centers. Notwithstanding the extraordinary efforts to ensure quality control of the two types of lymph node dissection, both noncompliance (not removing all lymph node stations) and contamination (removing more than was indicated) occurred, thus blurring the distinction between the two operations and confounding the interpretation of the oncologic end points.[196,198] The postoperative morbidity rate was higher in the D2 group (43% versus 25%; $p < 0.001$), the reoperation rate was also higher at 18% (59/331) versus 8% (30/380), and the mortality rate was also significantly higher in the D2 group (10% versus 4%; $p = 0.004$). Patients treated with D2 dissection also required a longer hospitalization.[199] As in the MRC trial, partial pancreatectomy and splenectomy were performed en passant in the D2 group. Five-year survival rates were similar in the two groups: 45% for the D1 group and 47% for the D2 group (95% CI for the difference = −9.6% to 5.6%). The subset of patients who had R0 resections, excluding those who died postoperatively, had cumulative risks of relapse at 5 years of 43% with D1 dissection and 37% with D2 dissection (95% CI for the difference = −2.4% to 14.4%).

The Dutch investigators concluded that there was no role for the routine use of D2 lymph node dissection in patients with gastric cancer. At 15-year follow-up, 174/711 (25%) patients were alive, all but one without recurrence. The OS was 21% (82/711) and 29% (92 patients) for the D1 and D2 groups, respectively ($p = 0.34$). Interestingly, gastric cancer–specific death was higher in the D1 group 48% (182/380) versus 37% (123/331). Local recurrence was higher in the D1 group 22% (82/380) versus 12% (40/331), and regional recurrence 19% (73/380) versus 13% (43/331). The authors concluded that after 15 years of follow-up, D2 lymphadenectomy is associated with lower locoregional recurrence and gastric cancer–specific death rates than D1 lymphadenectomy. D2 resection is also associated with higher postoperative mortality, morbidity, and reoperation rates. Examining the results after 15-year follow-up and given the data regarding gastric cancer–specific mortality, local recurrence, and regional recurrence, the authors revised their original conclusion: "Because spleen-preserving D2 resection is safer in high-volume centers, it is the recommended surgical approach for patients with potentially curable gastric cancer."[196]

Degiuli et al.[191] reported on the Italian Gastric Cancer Study Group experience with a prospective randomized trial comparing pancreas-sparing D1 versus D2. There were 76 patients randomized to undergo D1 and 86 D2 resections. Complication rates were higher in the D2 group: 16.3% versus 10.5%. Postoperative mortality was higher in the D1 group: 1.3% versus 0% in the D2 group. Thus far, no survival data are available. The authors concluded that, in experienced hands, the morbidity and mortality can be as low as shown by Japanese surgeons.

Wu et al.[192] reported on a randomized trial comparing D1 versus D3 dissections.[199] There were no operative deaths, and morbidity was only 12%. At median follow-up of 94.5 months, D3 showed better overall 5-year survival of 59.5% (95% CI = 50.3 to 68.7) versus 53.6% (95% CI = 44.2 to 63.0; $p = 0.041$), and a trend toward better DFS at 5 years: 40.3% versus 50.6% ($p = 0.197$). Only 13% had pancreas or splenic resection as compared with 23% in the Dutch trial. The authors concluded that D3 as compared to D1 offers survival benefit. As far as the authors of this chapter understand, this is the first RCT to demonstrate survival advantage for more extensive lymphadenectomy (D3). As such, it requires careful examination. Roggin and Posner[200] have critically reviewed the work by Wu et al.[192] One controversial element of this trial was the use of OS versus gastric cancer–specific survival; 17/111 (15%) of the reported deaths were not related to tumor recurrence, resulting in very small survival benefit.

Interpretation of the existing level 1 evidence is encumbered by a number of issues that have been discussed in detail elsewhere.[171,172] The primary concerns relate to whether (1) the increased operative

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TABLE 46.4

Prospective Randomized Trials Comparing D1 Versus D2 and D3 Resection for Potentially Curable Gastric Carcinoma

	Extent of Lymphadenectomy		
Study (Ref.)	**D1**	**D2**	***P* Value**
Groote Schuur Hospital, Cape Town, 1988[188]			
Number of patients	22	21	—
Length of operation (h)	1.7 ± 0.6	2.33 ± 0.7	<0.005
Transfusions (units/group)	4	25	<0.05
Postoperative stay (d)	9.3 ± 4.7	13.9 ± 9.7	<0.05
5-y overall survival (log rank test)	0.69	0.67	NS
Prince of Wales Hospital, Hong Kong, 1994[167]			
Number of patients	25	29	—
Length of operation (h)	140	260	<0.05
Operative blood loss (ml)	300	600	<0.05
Postoperative stay	8	16	<0.05
Median survival (d)	1,511	922	<0.05
Medical Research Council Trial, United Kingdom, 1999[189,193]			
Number of patients	200	200	—
Operative mortality (%)	6.5	13	<0.04
Postoperative complications (%)	28	46	<0.001
5-y overall survival (%)	35	3	NS
Dutch Gastric Cancer Trial, The Netherlands, 1999 (2009, 15-y F/U update)[190,196]			
Number of patients	380	331	—
Operative mortality rate (%)	4	10	0.004
Postoperative complications (%)	25	43	<0.001
Postoperative stay (d)	18	25	<0.001
5-y overall survival (%)	45	47	NS
11-y F/U overall survival (%)	30	35	0.53
11-y F/U survival (perioperative death excluded)	32	39	0.10
15y F/U overall survival	21	29	0.34
15y F/U gastric cancer–specific death	48	37	0.01
Italian Gastric Cancer Study Group, 2004[191]			
Number of patients	76	86	—
Operative mortality rate (%)	1.3	0	NS
Postoperative complication (%)	10.5	16.3	0.29
Postoperative stay (d)	12	12	NS
5-y overall survival	NS	NS	NS
Yang-Ming University, Taiwan, 2006[192]			
Number of patients	110	111, D3	
Operative mortality rate (%)	0	0	
Postoperative complication (%)	10.1	17.1	0.012
Postoperative stay (d)	15	19.6	0.001
5-y overall survival	53.6	59.5	0.041

NS, not stated; F/U, follow-up.

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mortality associated with protocol-mandated partial pancreatectomy and splenectomy for patients with proximal tumors undergoing D2 dissection prevented identification of a potential therapeutic impact of extended lymph node dissection, and (2) the phenomena of noncompliance and contamination led to homogenization of the operative procedures to such an extent that the fundamental hypothesis was not tested. Owing to these interpretation issues, the question of a possible therapeutic benefit of D2 dissection remains unsettled.

Many Japanese gastric surgeons have considered the caveats associated with the MRC and Dutch trials and believe that, notwithstanding inherent patient selection and stage migration biases,[171,196,198,201,202] the existing retrospective data provide sufficient proof of a clinical benefit of D2 dissection. On this basis, D2 dissection has been adopted as the standard of care for patients with localized, higher-risk gastric cancer in many centers in Japan and some specialized centers in the West.[203] The Japanese Clinical Oncology Group (JCOG-9501) has investigated an even more aggressive surgical approach in an RCT evaluating standard D2 versus D2-plus (para-aortic node dissection [PAND]) in the management of completely resected (R0) T2–4 gastric cancer.[204,205] Between July 1995 and April 2001, 523 patients from 25 institutions were registered. Patients were randomized intraoperatively to undergo D2 lymphadenectomy alone (263 patients) or D2 lymphadenectomy plus PAND (260 patients). The primary end point was OS. Postoperative morbidity was higher in the PAND group (28% versus. 21%; $p = 0.07$), and mortality was similar at 0.8% in each group. Five-year OS for patients undergoing PAND was 70.3% versus 69.2% (HR = 1.03; $p = 0.85$). There was no significant difference in recurrence-free survival. The authors concluded that, as compared to D2 lymphadenectomy, PAND when added to D2 lymphadenectomy does not improve survival rates.

Another Japanese study compared D2 with extended PAND (D4).[206] This trial randomized patients to undergo gastrectomy with D2 ($n = 135$) or D4 ($n = 134$) lymphadenectomy. The 5-year survival rates were 52.6% versus 55%, respectively ($p = 0.8$). The authors concluded that prophylactic D4 dissection is not recommended. In an RCT, a Western group from Poland investigated D2 dissection versus extended D2 dissection defined according to the Japanese Gastric Cancer Association classification.[207] They randomized 275 patients with gastric cancer to gastrectomy with D2 ($n = 141$) versus D2 + lymphadenectomy ($n = 134$). The overall postoperative morbidity and mortality were similar and did not differ statistically. Survival data are not available at this time.[207] Thus, the limits of radical surgery have been reached in Japan and the pendulum has swung back toward D2 dissection in clinical settings in which this can be safely performed.[201]

In summary, lymph nodes should be considered as indicators that the gate was opened rather than as the gate keepers for cure.[208] None of the prospective RCT trials executed in the West demonstrated survival advantage for more extensive lymphadenectomy. However, none of these studies were powered enough to detect single-digit difference in 5-year OS. Several non-a priori planned subgroup analyses were done and showed some survival advantage for certain subgroups. These analyses cannot be used to form evidence-based medicine, but should be used to form hypotheses for further RCT studies. In high-volume specialty centers, spleen- and pancreas-preserving D2 dissection is performed safely, and can potentially result in decreased gastric cancer–specific mortality based on 15 years of follow-up from the Dutch study (D2 37% versus 48%; $p = 0.01$).[196]

A recently published RCT from the multicenter Italian Gastric Cancer Study Group compared D1 to D2 lymphadenectomy for gastric adenocarcinoma with primary outcome of OS over median follow-up of 8.8 years.[209] There was no significant difference in OS (5-year OS = 66.5% versus 64.2%), operative morbidity (12% versus 17.9%), and mortality (3% versus 2.2%) in patients undergoing D1 and D2 gastrectomy; however, subgroup analysis suggested a trend toward improved disease-specific survival with D2 gastrectomy in patients with advanced T-stage (pT2-4) and node-positive disease (5-year disease-specific survival: D1 versus D2 = 38% versus 59%; $p = 0.055$).

A systematic review and meta-analysis of eight RCTs encompassing over 2,000 patients (D1, $n = 1,042$; D2, $n = 1,002$) evaluated the safety and efficacy of extended lymphadenectomy in gastric cancer.[210] A significant increase in operative morbidity and mortality was evident in patients undergoing extended D2 lymphadenectomy, with a trend in decreased disease-specific mortality in those having spleen- and pancreas-preserving gastrectomy. Longer-term survival is required to ascertain oncologically relevant outcome benefit with D2 gastrectomy.

Partial Pancreatectomy and Splenectomy Resect or Preserve? Partial (left, distal) pancreatectomy and splenectomy have been performed as part of D2 lymph node dissection to remove the lymph nodes along the splenic artery (station 11) and lymph nodes within the splenic hilum (station 12), primarily for patients with tumors located in the proximal and midstomach. Indeed, partial pancreatectomy and splenectomy were required for patients with proximal tumors in the D2 arm of the Dutch and MRC RCTs but were required only for direct tumor extension in the D1 arm. In the Dutch and MRC D1 versus D2 randomized trials, splenectomy was associated with increased risk of surgical complications and operative mortality. In addition, a multivariate analysis suggested that splenectomy is associated with inferior long-term survival. The frequent performance of splenectomy (e.g., 30% of patients in the D2 arm versus 3% in the D1 arms of the Dutch trial) in the patient undergoing extended D2 lymphadenectomy, with its associated adverse effects on both short- and long-term mortality, confounds the interpretation of the Dutch and MRC RCTs. Thus, the hypothesis that spleen- and pancreas-preserving D2 lymph node dissection improves survival remains unproven. There is an evolving consensus that splenectomy should be performed only in cases with intraoperative evidence of direct tumor extension into the spleen, or its hilar vasculature, or when the primary tumor is located in the proximal stomach along the greater curvature.[211] Partial pancreatectomy should be performed only in cases of direct tumor extension to the pancreas.

Recent reports have described pancreas- and spleen-preserving forms of D2 dissection.[212–218] This organ-preserving modification of classic D2 dissection allows for dissection of some station 11 and 12 lymph nodes without the potential adverse effects of pancreatectomy and/or splenectomy. In a small single-institution RCT recently reported from Chile, Csendes et al.[219] randomized 187 patients with localized proximal gastric adenocarcinoma to treatment by total gastrectomy with D2 lymph node dissection plus splenectomy or total gastrectomy with D2 lymphadenectomy alone. Operative mortality was similar in both groups (splenectomy group, 3%; control group, 4%). However, septic complication rates were higher in the splenectomy arm than in the control arm ($p < 0.04$). There was no difference in 5-year OS between study groups, although it is not clear that the trial was designed with survival as the primary end point. Other investigators confirmed these findings.[218,220,221]

The JCOG is conducting a multi-institutional RCT (JCOG 0110-MF) comparing D2 dissection with and without splenectomy for patients diagnosed with proximal gastric cancer.[222] The hypothesis to be tested is that 5-year OS of patients treated by extended D2 dissection *without* splenectomy is 5% less than that of patients treated by D2 dissection *with* splenectomy. With a planned accrual of 500 patients, this design will provide 70% power to reject the null hypothesis when 5-year OS is 3% greater following splenic preservation compared with splenectomy.[222] The results of this trial will better define the short- and long-term effects of splenectomy for patients with proximal gastric cancers undergoing extended lymphadenectomy.

In an effort to reduce operative morbidity and mortality without compromising oncologic outcome in patients undergoing

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extended lymphadenectomy for gastric adenocarcinoma, eight clinical trials have compared laparoscopic to open gastrectomy with D2 lymph node dissection. A meta-analysis was conducted of these eight trials, which enrolled nearly 1,500 patients with gastric cancer to assess the feasibility and safety of laparoscopic total gastrectomy with D2 lymphadenectomy compared to the same operation done in the standard open manner.[223] The laparoscopic technique was associated with significantly longer operative time, less operative blood loss, fewer analgesic requirements, earlier return of bowel function, shorter hospital stay, and reduced operative morbidity (relative risk = 0.70; 95% CI = 0.50 to 0.98; $p = 0.035$). The total number of lymph nodes removed surgically and analyzed pathologically as well as operative mortality was not significantly different between groups. Further well-designed clinical RCTs are warranted to define the role of laparoscopic gastrectomy and extended lymphadenectomy for gastric adenocarcinoma. (A more detailed discussion follows in the section titled "Minimally Invasive Surgery for Gastric Resection.")

Laparoscopy clearly has a role in the complete staging of disease in patients with gastric adenocarcinoma and the detection of radiologically occult macroscopic, or microscopic peritoneal cytology positive-only metastasis. Laparoscopy and peritoneal cytology are important for accurate staging and the detection of occult metastatic disease. This methodology adds value to modern imaging techniques, for positive microscopic peritoneal cytology-only disease is tantamount to macroscopic M1 disease in terms of oncologic outcome.

A recent international multidisciplinary expert panel created statements to define processes of care relevant to the perioperative management of patient with gastric cancer.[224] Ten processes were deemed essential to maintaining quality of care:

1. CT of the abdomen and pelvis is part of preoperative staging.
2. PET scans are not routinely indicated.
3. Adjuvant therapy should be considered.
4. Clinical trials should be conducted and patients considered for participation.
5. Treatment decision making should involve a multidisciplinary team.
6. Hospitals must have sufficient systems in place to support the care of patients with gastric cancer.
7. Sixteen or more lymph nodes should be resected and staged pathologically.
8. Surgery should only be performed to palliate major symptoms in the setting of metastatic disease.
9. Surgeons experienced in the treatment of gastric cancer should be performing the operations.
10. These surgeons should also have advanced laparoscopic surgery experience for laparoscopic gastric resection.

These processes were deemed to be of indeterminate necessity for maintaining quality of care:

1. Diagnostic laparoscopy before treatment
2. Multidisciplinary approach to patients with linitis plastica
3. Genetic testing for diffuse gastric cancer, family history, or age <45 years at time of diagnosis
4. Endoscopic removal of select T1aN0 lesions
5. D2 lymphadenectomy in curative intent cases
6. D1 lymphadenectomy for EGC or patients with comorbidities
7. Frozen section analysis of gastric resection margins
8. Nonemergent cases performed in a hospital with a volume of >15 gastric cancer resections per year
9. By a surgeon who performs more than six gastric resections per year

Individualized Assessments of Lymph Node Involvement.

Recent attention has focused on methods of individual assessment of risk of lymphatic spread. These techniques offer the possibility of tailoring surgical therapy for an individual patient based on clinicopathologic risk assessment of the primary tumor and/or preoperative or intraoperative identification of SLNs, or primary draining lymph nodes. At present, at least three approaches to individual nodal risk assessment have been evaluated: computer modeling, preoperative endoscopic peritumoral injection, and SLN biopsy.

Preoperative Computer Modeling of Individual Patient Nodal Involvement. Kampschoer et al.[225] have developed a computer program to estimate the probability of spread to specific nodal regions for an individual patient using his or her pretreatment clinicopathologic data. The program incorporated data on tumor size, depth of infiltration, primary tumor location, grade, type, and macroscopic appearance of primary tumors from 2,000 patients with surgically resected gastric cancers treated at the National Cancer Center of Tokyo. The data set used for matching individual patient data is continuously updated and now includes >8,000 patients. This computer model has been validated in non-Japanese patients in Germany[226] and Italy.[227] In the United States, Hundahl et al.[228] retrospectively applied this computer model to evaluate the surgical treatment of patients entered into the intergroup trial of adjuvant 5-FU–based chemoradiation. The Kampschoer et al.[225] program was used to estimate the likelihood of disease in undissected regional node stations, defining the sum of these estimates as the Maruyama index of unresected disease. Fifty-four percent of participating patients underwent D0 lymphadenectomy. The median index was 70 (range = 0 to 429). In contrast to D level, the Maruyama index proved to be an independent prognostic factor of survival, even with adjustment for the potentially linked variables of T stage and number of positive nodes. More recent and smaller studies confirmed these findings.[229–231]

Preoperative Endoscopic Peritumoral Injection. The hypothesis that peritumoral injection of compounds designed to optimize lymph node dissection improves lymph node clearance was addressed in a small RCT evaluating preoperative endoscopic vital dye staining with CH40 prior to D2 dissection. The frequency of positive lymph nodes in patients injected with CH40 before D2 dissection was greater than that observed in patients treated by D2 dissection alone.[232] This approach optimized the yield of lymph node dissection presumably by directing surgeons to include specific lymph nodes in the dissection that might have otherwise been left in situ and/or by directing pathologists to examine specific areas of the lymphadenectomy specimens. Further prospective studies of this approach are required to confirm the feasibility of this technique and to assess its impact on intraoperative decision making regarding the extent of lymphadenectomy and accuracy of specimen dissection and nodal retrieval in anatomic pathology.

Sentinel Lymph Node Biopsy. The goal of SLN biopsy is to identify the node or nodes believed to be the first peritumoral lymph nodes in the orderly spread of gastric adenocarcinoma from the primary site to the regional lymph nodes. Sampling of this lymph node(s) may allow for prediction of the nodal status of the entire lymph node basin, possibly obviating extended nodal dissection and its attendant morbidity in patients found to have a negative SLN. Recent pilot studies have evaluated the feasibility, sensitivity, and specificity of SLN biopsy for patients with gastric cancer.[233–242] These pilot studies demonstrated that SLN identification is feasible in approximately 95% of patients. However, most patients with gastric cancer have multiple "sentinel" nodes, with mean numbers of SLNs per patient ranging from 2.6 to 6.3. The aggregate experience to date suggests that among patients with pathologically involved lymph nodes, SLN results in false-negative assessment of pathologic regional nodal status in 11% to 60% of patients. Thus, the preliminary data available suggest that SLN biopsy cannot reliably replace lymph node dissection as a means of accurately staging regional nodal basins in gastric adenocarcinoma.[243–247]

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In a large study of nearly 400 patients, the ability and accuracy of SLNs was examined in a prospective, multicenter phase 2 study.[248] Patients with early T stage gastric cancer (cT1 or cT2, tumor <4 cm) were evaluated with SLN mapping, followed by gastrectomy and D2 dissection. The SLN mapping technique identified 57 patients who had nodal involvement, of which 53 had true positive SLNs, resulting in 99% accuracy. Though further validation is needed, these results are quite encouraging.

The JCOG multicenter trial (JCOG-0302) assessed the feasibility and accuracy of indocyanine green (ICG) SLN mapping at time of surgery prior to gastrectomy and lymphadenectomy for EGC (T1).[249] Single sections of ICG-stained SLNs were examined intraoperatively using frozen section with hematoxylin and eosin stain. The primary study end point was the proportion of false-negative SLNs. Study accrual was halted after 440 of the planned 1,550 patients were enrolled when the proportion of false negatives was found to be unexpectedly and unacceptably high (46%). The authors appropriately concluded that SLN mapping and biopsy using ICG and intraoperative single nodal frozen section evaluation using hematoxylin and eosin staining is inappropriate for clinical use in EGC.

Volume-Outcome Relationships for Gastrectomy. Recent studies have established a clear relationship between institutional gastrectomy volume and perioperative mortality rates—the so-called volume-outcome relationship. The recent analysis of a national database by Birkmeyer et al.[250–252] of 31,854 patients who underwent gastrectomy between 1994 and 1999 demonstrated an inverse relationship between institutional gastrectomy volume and operative mortality rates. The odds ratio for gastrectomy-related death was lowest among patients treated within hospitals in the highest gastrectomy volume quintile (odds ratio = 0.72; 95% CI = 0.63 to 0.83). A separate analysis evaluating surrogate end points for morbidity demonstrated that gastrectomy at high-volume centers was associated with the shortest duration of hospital stay and the lowest readmission rates.[253–256] Similar findings were noted by Hannan et al.[257] in an analysis of the New York State Department of Health's administrative database. Their analysis of 3,711 patients who underwent gastrectomy between 1994 and 1997 included adjustments for covariates such as age, demographic variables, organ metastasis, socioeconomic status, and comorbidities. Patients who had a gastrectomy at hospitals in the highest-volume quartile had an absolute risk-adjusted mortality rate that was 7.1% (p <0.0001) lower than those treated at hospitals in the lowest-volume quartile, although the overall mortality rate for gastrectomy was only 6.2%.

These studies demonstrate that the risk-adjusted mortality rates for gastrectomy are significantly lower when gastrectomy is performed by high-volume providers.[258–261] It is likely that the variations in gastrectomy-related mortality rates relate in part to surgeon training and their patient age-volume[262–264] and experience with the procedure. Data on gastrectomy volume obtained from general surgeons undergoing recertification after a minimum of 7 years in practice demonstrate that the mean number of gastric resections performed by recertifying general surgeons in the United States is only 1.4 per year.[265] Thus, given the data supporting a relationship between hospital and provider volumes and the morbidity and mortality rate of gastric resection, there are reasons to consider regionalization of the surgical treatment of gastric cancers.

Outcome in Japan Versus Western Countries. Stage-stratified survival rates for gastric adenocarcinoma are higher in Japan than in most Western countries. The reasons for this are complex, are incompletely understood, and cannot be fully addressed within the context of a chapter covering all aspects of gastric cancers.

Important differences in the epidemiology of gastric cancer may contribute to observed differences in outcome in Japan versus Western countries. First, the better-prognosis intestinal-type (Laurén classification)[266] tumors are seen more commonly in Japan, whereas the diffuse-type cancers (poorer prognosis) are more frequent in Western series. These regional differences in the frequencies of intestinal and diffuse cancers are believed to be related to the higher incidence of *H. pylori* infection and atrophic gastritis in Japan. Second, poorer-prognosis proximal gastric cancers are less frequent in Japan.[267–269] Indeed, the progressive increase in proximal gastric cancers observed in the West has not been observed in Japanese populations.

Regional differences in the diagnostic criteria for EGC also may contribute to regional differences in observed outcome. In Japan, gastric carcinoma is diagnosed based on its structural and cytologic features without consideration of invasion of the lamina propria. In contrast, Western pathologists consider invasion of the lamina propria to be an essential element of the diagnosis of carcinoma.[270–274] As a consequence, unequivocally neoplastic noninvasive lesions are classified as carcinoma in Japan, but as dysplasia by Western pathologists.[270] To overcome these differences, the Padvova,[275] Vienna,[276] and Revised Vienna[276] classifications have recently been proposed. However, until there is worldwide consensus and implementation of uniform diagnostic criteria for EGC, comparative assessments of the outcome of patients with EGC treated in Japan and Western countries should acknowledge the selection bias associated with different diagnostic criteria.

Stage migration is a well-documented factor contributing to the stage-specific differences in outcome between Japanese and Western patients.[277] Stage migration arises because there is widespread use of extensive D2 or D3 lymphadenectomy combined with rigorous pathologic assessment of the lymphadenectomy specimen in Japan. More accurate stage assignment of Japanese patients leads to secondary stage migration—improvement in stage-specific survival without improvement in OS. The frequency and impact of stage migration were quantified by the Dutch Gastric Cancer Group in their RCT comparing D1 and D2 lymph node dissection.[190,278] Stage migration occurred in 30% of patients in the D2 group, and the stage-specific decreases in survival rates attributable to stage migration were 3% for AJCC/UICC stage I disease, 8% for stage II, 6% for stage III, and 12% for stage IIIB, with the more accurately staged D2 group having higher survival rates.[278]

In addition to regional differences in epidemiology, diagnostic criteria for EGC, and stage migration, other factors may contribute to the observed differences in stage-stratified survival. Such factors may include genetic, environmental, and biologic differences between Japanese and Western patients and tumors. These factors have been less well studied, but were addressed in a comprehensive review by Davis and Sano.[279]

Outcome in Korea Versus Western Countries. A separate evaluation was performed comparing gastric cancer survival following curative intent resection in Korea versus the United States.[126] This study compared two independent, single-institution prospectively maintained databases from 1995 to 2005: one from MSKCC (n = 711 curatively resected patients who did not receive neoadjuvant therapy) and another from St. Mary's Hospital in Seoul, South Korea (n = 1,646 patients, also curatively resected without receiving preoperative therapy). All patients had a D2 dissection and adequate nodal staging. There were notable differences in the two cohorts: patients from the United States were more likely to have proximal tumors and more advanced stage compared with patients resected in Korea. However, when controlling for all known risk factors, stage for stage, patients from Korea still had better OS (HR = 1.3; 95% CI = 1.0 to 1.7; p = 0.05). These data cannot exclude differences in underlying cancer biology as a potential explanation for the observed differences in survival in gastric cancer between patients treated in Korea versus those treated in the United States.

Minimally Invasive Surgery for Gastric Resection

The utilization of laparoscopy in gastric surgery has been increasing over the past decade. There are a plethora of non-RCTs reporting on laparoscopic distal gastrectomy, total gastrectomy, and D2

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dissection, and practically every open procedure has been tested using laparoscopy. We will review here the available data from published RCTs. There are no RCTs reporting on total gastrectomies.[280] None of the current RCTs reporting on laparoscopy in gastric cancer are of sufficient quality and magnitude to be considered "practice changing." Huscher et al.[281,282] reported on the largest RCT testing laparoscopic ($n = 29$) versus open ($n = 30$) subtotal gastrectomy for distal gastric cancer. After 5 years of follow-up, overall morbidity and mortality were equivalent. Laparoscopic resection resulted in less blood loss, shorter hospital stay, longer operative time, and earlier resumption of oral intake; these were reported by other authors as well.[283,284] There was no difference in the number of lymph nodes harvested. Overall 5-year and DFS did not differ significantly. The authors concluded that laparoscopic subtotal gastrectomy is feasible and has similar short- and long-term outcomes as open surgery.

Kim et al.[285] reported on laparoscopy-assisted distal gastrectomy (LADG) versus open distal gastrectomy (ODG) for early gastric cancer. This trial was designed to test the 5-year survival utilizing noninferiority design. The interim analysis showed less blood loss ($p < 0.001$), reduced amount of analgesic used ($p < 0.019$), shorter hospital stay ($p < 0.0001$), fewer number of lymph nodes harvested in the LADG arm ($p < 0.05$), and improved short-term quality of life (QOL) parameters on global health ($p < 0.0001$). The authors concluded that comparison of LADG with ODG resulted in improved QOL outcomes in patients followed up to 3 months. The authors have now reported long-term follow-up data.[286] In this study, the authors evaluated 2,976 patients who were treated with either laparoscopic gastrectomy (1,477 patients) or open gastrectomy (1,499 patients) between April 1998 and December 2005. With a median follow-up of 70.8 months, there was no difference in survival between the two resection methodologies, with the exception that for stage IA gastric cancer, laparoscopic gastrectomy had a improved survival (95.3% 5-year survival) versus open gastrectomy (90.3% 5-year survival) ($p < 0.001$).[286] Recently, Ohtani et al.[287] performed meta-analysis of RCT that compared LADG versus ODG for EGC. Their report confirmed the results from Kim et al.[286] and Lee and Han.[288]

A recent update and meta-analysis analyzed data on 784 patients enrolled in eight RCTs[289] comparing laparoscopy-assisted to open gastrectomy for resectable gastric cancer. Despite the fact that operative time was significantly prolonged in the laparoscopy group and that analgesic use, operative blood loss, nodal yield, morbidity (overall and anastomotic), and mortality were *no* different when compared with open gastrectomy, there were a number of clinically important benefits observed in those undergoing minimally invasive surgery. Pulmonary morbidity (odds ratio = 0.43; 95% CI = 0.20 to 0.93; $p = 0.03$), duration of postoperative ileus (missing data = −0.23; 95% CI = −0.41 to −0.05), and hospital stay (missing data = −1.72; 95% CI = −3.40 to 0.04) were significantly reduced in the laparoscopy-assisted gastrectomy group. The survival benefit of minimally invasive surgery in resectable gastric cancer has yet to be definitively demonstrated.[289]

Laparoscopy is another tool in the armamentarium of the surgical oncologist. The question is not whether it can be done laparoscopically, certainly it can; the question is whether it should be done in patients with gastric adenocarcinoma. Recently, a meta-analysis of six clinical trials (658 patients) compared laparoscopic versus open gastrectomy for distal EGC.[290] In this analysis, the authors noted significant reductions in postoperative complications and length of hospital stay in the laparoscopic group, whereas the open gastrectomy group had less operating time and a greater number of lymph nodes harvested. There were no notable differences in the time to return of bowel function, incidence of wound infection, postoperative abscess formation, or anastomotic leak or pulmonary complications, suggesting that there may be some advantages of the laparoscopic approach. The oncologic equivalence, however, has not been adequately tested. Whether the energy, time, and capital invested in developing laparoscopic surgery for gastric cancer is worth it is the relevant question particularly in an era of skyrocketing medical costs. Certainly, beyond the short term there seems to be no advantage of laparoscopic surgery in gastric cancer. In view of the reported morbidity and mortality in specialty centers, the advantage gained by laparoscopic gastric resection over the first few days underlines the question of whether we should invest more in innovative therapies to eradicate gastric cancer than the simple technical aspects of noninvasive extirpative surgery.

A large prospective random assignment study from Korea is underway in which 1,415 patients with EGC (pT1-2 N0) are randomly assigned to receive either open or laparoscopic distal gastrectomy.[291] Final results of this expected "definitive" phase 3 study are expected to be available in September 2015. A similar large phase 3 study for stage IA and stage IB gastric cancer was initiated in Japan in March 2010. This study randomizes 920 patients from 33 institutions, with the primary end point of OS.[292] Together, it is anticipated that these two pivotal studies will definitively define the role of laparoscopic-assisted gastrectomy in EGC.

Adjuvant Therapy

Patients with EGCs (e.g., patients with AJCC stage I and some stage II) have a good chance of cure with surgery alone. However, the Japanese S-1 adjuvant study indicates that the prognosis for even stage II tumors can be improved with systemic chemotherapy.

Adjuvant therapy indicates administration of a treatment following a potential curative resection of the primary tumor and regional lymph nodes. Therapy after resections that leave microscopic or gross disease are not adjuvant treatment, but rather therapy for known disease, which is palliative in nature. Neoadjuvant chemotherapy involves the use of systemic treatment before potentially curative surgery.

There are several theoretical reasons for beginning adjuvant therapy soon after operation (perioperative chemotherapy). Studies have shown a rapid increase in cell growth of metastases after a primary tumor has been removed related to a decline in certain circulating factors, which serve to inhibit angiogenesis or other cell-cycle promotors, once the primary tumor is removed. Perioperative or neoadjuvant chemotherapy has been studied because the ability to perform a R0 resection in gastric cancer is difficult. In addition, a substantial number of patients undergoing gastrectomy have prolonged recovery. Neoadjuvant chemotherapy has a dual goal: allowing a higher rate of R0 resections and treatment of micrometastatic disease early in the course of treatment.

Adjuvant Systemic Therapy. The results of selected recent RCTs comparing adjuvant chemotherapy with surgery alone are summarized in Table 46.5. Japanese investigators studied S-1, an oral fluoropyrimidine, in a group of 1,059 patients (stages II to IIIB). S-1 was given for 12 months (4 weeks on/2 weeks off). A total of 529 patients received S-1 plus operation and 530 patients underwent operation only. The 3-year OS was 80.1% and 70.1%, respectively (HR = 0.68).[293]

The 5-year survival update was recently reported and demonstrated a sustained benefit in 5-year OS of 71.7% with adjuvant S-1 versus 61.1% with surgery alone (HR = 0.669; 95% CI = 0.540 to 0.828).[294] In addition, another Asian study from Korea reported the results of adjuvant capecitabine and oxaliplatin.[295] In this study, patients were required to have a D2 resection, and those with stage II-IIIB were then randomly assigned to receive 6 months (eight cycles) of capecitabine/oxaliplatin or observation. This was a large study, in which 520 patients were randomly assigned to receive adjuvant chemotherapy and 515 to surgery alone. The study met its primary endpoint of 3-year DFS (74% [95% CI = 69 to 79] with chemotherapy versus 59% [53% to 64%] with surgery alone; $p < 0.0001$). In contradistinction to the positive results using S-1, and the MAGIC and ACCORD 07 trials described later, Di Costanzo et al.[296] did not find a benefit to the use of cisplatin, epirubicin, leucovorin, and 5-FU as adjuvant therapy.

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TABLE 46.5

Adjuvant Therapy for Gastric Cancer: Phase 3 Trials

Study (Ref.)	No. of Patients	Three-y DFS (%)	Overall 5-y Survival (%)	HR
S-1[293]				
Surgery	530	60	70	
Adjuvant	529	72	80	0.38
INT-116[339]				
Surgery	275	31	41	1.35
Adjuvant	281	48	50	
GOIRC[296]				
Surgery	128	42[a]	49	0.90
Adjuvant	130	43[a]	48	
MAGIC[327]				
Surgery	253	25	23	0.75
Neoadjuvant	250	38	36	
ACCORD-07[318]				
Surgery	111	25	21	0.69
Neoadjuvant	113	40	34	

DFS, disease-free survival; HR, hazard ratio; INT, Intergroup Trial; GOIRC, Gruppo Oncologico Italiano di Ricerca Clinica; MAGIC, Medical Research Council Adjuvant Gastric Infusional Chemotherapy; ACCORD, the French Action Clinique Coordonnées en Cancérologie Digestive.
[a] Five-year DFS.

Several meta-analyses of adjuvant chemotherapy in gastric cancer have been reported. Recently, Buyse et al.[297] reported a meta-analysis that included individual patient data; 16 trials involving 3,710 patients were available for analysis. They found an OS benefit in favor of adjuvant chemotherapy (HR = 0.83; 95% CI = 0.76 to 0.91; p <0.0001). The absolute benefit was 6.3% at 5 years. The GASTRIC group conducted a meta-analysis; as of 2010, individual patient data for 17 trials involving 3,838 patients were available for analysis. They found an OS benefit in favor of adjuvant chemotherapy (HR = 0.82; 95% CI = 0.75 to 0.90; p >0.001). The absolute benefit was 5.9% at 5 years.[298] Shown in Table 46.5 are the results of recent trials in which adjuvant chemotherapy plus potentially curative resection was studied. The five most recent trials indicate that adjuvant therapy decreases the risk of recurrence by approximately 10%.[299] The use of systemic therapy plus potentially curative resection is considered a standard of care for patients with locally advanced gastric cancers. The most effective regimen to use, whether or not it is best to give therapy perioperatively, and the role of postoperative radiation *plus* systemic therapy are the focus of ongoing clinical research trials.

Adjuvant Intraperitoneal Chemotherapy. Peritoneal recurrence is a common pattern of failure for patients with gastric cancer, even after curative resection.[31,298] The median survival time of patients with peritoneal recurrence is 3 to 6 months. The rationale is based on the observation that drug concentrations within the peritoneal cavity are much higher than those achievable by intravenous or oral drug adminsitration. The data are a mixture of retrospective reviews, pilot phase 2 trials, and several small phase 3 trials. No definitive conclusions can yet be drawn regarding the effectiveness of intraperitoneal postoperative chemotherapy in this setting.

There are several modes of administering intraperitoneal chemotherapy: hyperthermic intraoperative peritoneal chemotherapy (HIPEC), normothermic intraoperative chemotherapy (NIIC) given at the conclusion of the operation, early postoperative intraperitoneal (normothermic) chemotherapy (EPIC), or delayed postoperative intraperitoneal (normothermic) chemotherapy. The theoretical advantage of intraoperative treatment is better drug distribution and the ability to use hyperthermia (HIPEC) to enhance microscopic tumor cytotoxicity. Most trials in gastric cancer have used either 5-FU or floxuridine, mitomycin C, or cisplatin for intraperitoneal chemotherapy.[300–309] Yan et al.[310] performed a meta-analysis of the RCTs reporting on adjuvant intraperitoneal chemotherapy for patients undergoing curative gastric resection; 10 trials involving 1,474 patients were included. A total of 775 patients had resection alone, and 873 patients had resection plus intraperitoneal treatment. A significant improvement in survival was associated with HIPEC (HR = 0.6; 95% CI = 0.43 to 0.83; p = 0.002) or HIPEC plus EPIC (HR = 0.45; 95% CI = 0.29 to 0.68; p = 0.0002). There was only a trend toward survival benefit with NIIC (p = 0.06), but this was not significant with either EPIC alone or delayed postoperative intraperitoneal (normothermic) chemotherapy. The authors concluded that HIPEC with or without EPIC after curative gastric resection is associated with modest improvement in survival and increased complication rate.

Recently, Kang et al.[311] reported on 640 patients with serosal-positive gastric cancer who underwent resection and were then randomized to receive intravenous mitomycin-C (20 mg/m^2) at 3 to 6 weeks after surgery and oral doxifluridine (460 to 600 mg/m^2 per day) starting 4 weeks after the administration of mitomycin-C and continuing for 3 months, or to receive intraoperative intraperitoneal cisplatin (100 mg), intravenous mitomycin-C (15 mg/m^2) on postoperative day 1, followed by oral doxifluridine for 12 months, and six monthly intravenous cisplatin (60 mg/m^2). Results indicated potential improvement in progression-free survival (PFS) and OS for the intraperitoneal cisplatin therapy arm. Kuramoto et al.[312] reported in a retrospective fashion that extensive intraperitoneal lavage performed with 10 L of normal saline after curative resection and before NIIC is superior to surgery alone or to surgery plus NIIC.

Immunochemotherapy

The use of adjuvant immunostimulants given in combination with cytotoxic chemotherapy (immunchemotherapy) has been studied primarily in Asia. The detailed results of these trials have been discussed in the previous edition of this textbook. Although the data available suggest that immunochemotherapy may be valuable, larger and adequately powered clinical trials are necessary to evaluate the clinical utility and efficacy this approach.

Perioperative and Neoadjuvant Chemotherapy. Perioperative (pre- and postoperative) or neoadjuvant chemotherapy is an attractive concept in gastric cancer because many patients have locally advanced tumors at diagnosis, particularly in Western countries. There are two goals of perioperative treatment: to increase the likelihood of an R0 resection, and treat micrometastatic disease early. After gastric resection, many patients have a prolonged recovery, delaying initiation of adjuvant therapy. Phase 2 trials involving either purely preoperative or perioperative treatment demonstrated that there was no increase in anticipated surgical morbidity or mortality when compared to controls.[313,314] Brenner et al.[314] reported on patients with locally advanced, high-risk gastric cancer who received preoperative CF followed by intraperitoneal chemotherapy after resection. At 43 months of follow-up, 39.5% of patients were still alive. Evaluating efficacy at the primary site is difficult in gastric cancer. Kelsen et al.[313] compared EUS with pathologic stage in assessing objective regression after neoadjuvant chemotherapy. They found that even though EUS was an accurate test in previously untreated patients following administration of chemotherapy, after chemotherapy and prior to surgery, EUS was inaccurate in measuring the depth of invasion (T stage) or lymph node involvement.

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FDG-PET scan as a predictive marker of response to preoperative chemotherapy has been studied in patients with gastric cancer. Ott et al.[77] reported on 44 patients with locally advanced gastric cancer who underwent PET scans prior to and after receiving chemotherapy. A decreased SUV was able to differentiate between patients who responded pathologically to treatment and those who did not.[315] These data suggest that functional imaging may eventually prove to be a useful predictive marker for efficacy. Studies in which systemic therapy is changed on the basis of an early PET scan are now under way. As previously noted, for patients with gastric cancer, approximately 20% to 25% of patients will not have an informative PET scan, so this technique cannot be used as a predictive marker for these patients.

FDG-PET and PET/CT scan are being evaluated in Japan as a potentially useful modality for the purpose of gastric cancer. A recently published trial from the National Center for Global Health and Medicine in Tokyo studied over 150,000 asymptomatic patients as part of it FDG-PET screening.[316] With a sensitivity and positive predictive value of 38% and 34%, respectively, the authors appropriately concluded that gastric endoscopy should be included as part of screening programs in order to increase rate of gastric cancer detection.[316]

After phase 2 studies demonstrated safety and suggested efficacy, several perioperative chemotherapy phase 3 trials were conducted (see Table 46.5). English investigators led by Cunningham et al.[317] reported the final results of a well-designed, random assignment study comparing surgery alone with surgery and perioperative chemotherapy in patients with gastroesophageal junction and gastric cancers (the MAGIC trial). All patients had potentially resectable disease prior to entrance into the study. Patients assigned to perioperative chemotherapy were treated with the epirubicin-cisplatin–5-FU (ECF) regimen. Chemotherapy was given both before and after surgery. A total of 503 patients were entered into the study; three-quarters had gastric cancer and one-quarter had gastroesophageal junction or lower esophageal adenocarcinomas. The ECF chemotherapy was well tolerated, with no increase in surgical morbidity or mortality. There was a shift to an earlier stage overall in patients receiving perioperative chemotherapy, as well as an improved R0 resection rate. With a median follow-up of 4 years, there was a significant improvement in both disease-free and OS for patients receiving perioperative chemotherapy: 5-year survival rate was 36% for those receiving perioperative chemotherapy and 23% for those receiving surgery alone (HR = 0.75; 95% CI = 0.6 to 0.9; $p = 0.009$). The authors concluded that ECF perioperative chemotherapy improves outcome for patients with resectable gastric cancer without increasing operative morbidity or mortality. This important trial was a well-designed, adequately powered study demonstrating an advantage of systemic treatment plus surgery when compared with operation alone.

More recently, French investigators reported the results of a similar trial (ACCORD 07-FFCD 9703) using CF prior to surgery versus surgery alone.[318] Approximately half the patients receiving preoperative chemotherapy also received postoperative treatment using the same regimen. The results were similar to those of the MAGIC trial, with 5-year OS being 24% for those undergoing operation alone versus 30% for those who received perioperative chemotherapy. There was a similar improvement in DFS. The results of the ACCORD 07 trial support the results of the MAGIC study.

Summary for Neoadjuvant Chemotherapy. The results of the MAGIC and ACCORD 07 trials have shown that systemic chemotherapy regimens that are only modestly effective in palliating patients with advanced disease can have a small but clinically meaningful effect on survival when given in the perioperative setting. New and potentially effective cytotoxic agents as well as new biologic agents are now being introduced in the treatment of patients with gastric malignancy. Studies involving perioperative chemotherapy using these agents are now in the advanced planning stage. The results of the perioperative chemotherapy, MAGIC and ACCORD 07, trials and of postoperative S-1, and Intergroup Trial (INT 0116) chemoradiation studies support the use of systemic therapy as an important component of the treatment plan for patients with locally advanced gastric cancers. The best strategy to pursue—that is, whether to give systemic therapy first followed by operation or to proceed directly to operation followed by systemic treatment plus or minus radiation given after surgery—has yet to be determined.

Given that the role of neoadjuvant chemotherapy in gastric cancer remains controversial, a systematic review and meta-analysis of six RCTs (aggregate $n = 781$) was conducted to gain insights about the potential benefit of neoadjuvant chemotherapy followed by surgery as compared to surgery alone.[319] Outcomes analyzed in this meta-analysis were OS, rate of R0 resection, downstaging effect of neoadjuvant chemotherapy, operative morbidity, and mortality. No significant difference were evident when comparing neoadjuvant chemotherapy and surgery to surgery alone for these outcome variables; odds ratios were as follows for OS 1.16 (0.85 to 1.58; $p = 0.36$), R0 resection 1.24 (0.78 to 1.96; $p = 0.36$), operative morbidity 1.25 (0.75 to 2.09; $p = 0.39$), and mortality 3.60 (0.59 to 22.45; $p = 0.17$).

Adjuvant Radiation and Chemoradiation Therapy. The recognition of the high rates of local and regional failure following surgery in patterns of failure analyses has served as the basis for clinical trials assessing the value of radiation therapy with and without chemotherapy as an adjuvant treatment in gastric cancer. Although these studies have all addressed the important question of whether clinical outcome is enhanced by adjuvant radiation therapy, there has been marked variability in radiation dose and schedule, sequence with surgery (preoperatively, intraoperatively, or postoperatively), and the use of concurrent and maintenance chemotherapy. These differences in study design may explain in part the conflicting results observed in phase 3 studies.

Two randomized phase 3 trials have studied the use of external beam radiation therapy (EBRT) alone with surgery.[320–322] Although both studies used similar radiation dose and schedule, sequence with surgery differed. In the British Stomach Cancer Group study, 436 patients were randomized to surgery alone, postoperative radiation therapy (45 to 50 Gy in 25 to 28 fractions), or cytotoxic chemotherapy with mitomycin, doxorubicin, and 5-FU.[320,321] The 5-year survival for surgery alone was 20%, for surgery plus radiation therapy 12%, and for surgery plus chemotherapy 19%. In this study, no survival advantage was observed for patients who received postoperative EBRT, although there was an apparent improvement in local control, demonstrating that local disease could be affected by adjuvant radiation therapy. Locoregional failure was documented in only 15 of 153 (10%) in the radiation arm versus 39 of 145 (27%) in the surgery-alone arm, and 26 of 138 (19%) in the mitomycin, doxorubicin, and 5-FU group. Interpretation of these results is complicated by the inclusion of 171 patients undergoing resection with gross or microscopic residual carcinoma. These patients would not be candidates for current gastric surgical adjuvant trials in the United States. In addition, approximately one-third of patients randomized to receive adjuvant treatment did not receive the assigned therapy. Of 153 patients randomized to the postoperative radiation arm, only 104 (68%) received a dose of 40.5 Gy or more, and 36 (24%) received none.

In contrast, the results of a phase 3 study from Beijing demonstrated a survival benefit for patients with gastric cardia carcinoma receiving preoperative radiation and surgery versus surgery alone.[322] In this study, 370 patients with gastric cardia carcinoma were randomized to 40 Gy in 20 fractions over 4 weeks of preoperative irradiation and surgery or surgery alone. The 5-year survival rates of preoperative radiation and surgery and the surgery-alone group were 30% and 20%, respectively (10-year, 20% and 13%, respectively; $p = 0.009$). Further, both local and regional nodal control was improved in patients undergoing preoperative radiation and surgery (61% and 61%, respectively) versus surgery

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(48% and 45%, respectively) only. Morbidity and mortality rates were not increased in patients receiving preoperative therapy.[323]

As the price role of adjuvant radiation in resectable gastric cancer remains controversial, an updated systematic review and meta-analysis of 13 RCTs[324] was conducted to gain insights about the potential benefit of adjuvant (including neoadjuvant) radiation and surgery versus surgery alone for resectable gastric cancer.[323] Outcomes analyzed in this meta-analysis were OS, and DFS. Postoperative radiation was associated with a significant improvement in both OS (HR = 0.78; 95% CI = 0.70 to 0.86; p <0.001) and DFS (HR = 0.71; 95% CI = 0.63 to 0.80; p <0.001). Similar improvement in OS (HR = 0.83; 95% CI = 0.67 to 1.03; p = 0.087) and DFS (HR = 0.77; 95% CI = 0.91 to 0.65; p = 0.002) was observed in five RCTs comparing surgery + adjuvant chemoradiation to surgery + adjuvant chemotherapy for resectable gastric cancer. This meta-analysis suggests that radiation following gastrectomy translates to ~20% DFS and OS benefit.

An alternative approach to postoperative or preoperative radiation is intraoperative radiation therapy (IORT).[325] The advantage of this technique is the ability to deliver a single large fraction (10 to 35 Gy) of radiation to the tumor or tumor bed while excluding or protecting surrounding normal tissue from the high-dose field. This approach permits high-dose radiation with minimal normal tissue treatment. Two randomized trials have examined the efficacy of IORT in combination with surgery for patients with gastric carcinoma.[326,327] Abe et al.[326] from Kyoto University performed a randomized trial of 211 patients with gastric cancer comparing surgery alone with surgery and IORT (28 to 35 Gy). For patients with tumor confined to the gastric wall (stage I), 5-year survival rates were similar for IORT and for resection alone. However, patients with Japanese stages II to IV disease who received IORT in conjunction with resection showed improved survival over patients who underwent resection without radiation. Among patients with stage IV disease (who usually had local residual disease after maximal resection), there were no 5-year survivors who received surgery alone; however, 15% of the patients who received IORT were alive at 5 years. The experience with IORT in gastric cancer at Kyoto University suggested that IORT may be beneficial in the treatment of locally advanced carcinoma of the stomach.

To further evaluate this approach, Sindelar et al.[327] at the National Cancer Institute conducted a prospective RCT comparing surgical resection and IORT with conventional therapy in gastric carcinoma. Patients in the experimental group underwent gastrectomy, and IORT was administered to the gastric bed (20 Gy). Patients in the control group underwent resection and postoperative EBRT to the upper abdomen (50 Gy in 25 fractions) for advanced-stage cancers extending beyond the gastric wall. Of the 100 patients screened for the study, 60 were randomized and underwent exploratory surgery. Nineteen patients were excluded intraoperatively because of unresectability or metastases, leaving 41 patients in the study. The median survival for patients with tumors of all stages was 25 months for the IORT group and 21 months for the control group (p = NS). Locoregional disease relapse occurred in 7 of 16 IORT patients (44%), and in 23 of 25 patients (92%) control patients (p <0.001). Complication rates were similar between IORT and control patients. Although IORT was not associated with a significant advantage over conventional therapy in terms of OS, IORT did significantly improve locoregional disease control. Based on these results, the use of IORT in gastric cancer remains investigational.

Because of the promising results in the early studies of combined-modality therapy for locally advanced (unresectable) or subtotally resected gastric cancer, investigators also have studied this combination of surgery and radiation in resectable gastric carcinoma. A small study from South Africa randomized 66 patients with resected gastric cancer (T (1–3), N (1–2), M0) to low-dose postoperative radiation (20 Gy in eight fractions over 10 days) and 5-FU, or to no further therapy after surgery.[328] No difference in survival was observed between the patients undergoing surgery and adjuvant therapy and those undergoing surgery alone. Given the subtherapeutic doses of radiation used in this study, it is difficult to draw any definitive conclusions as to the efficacy of adjuvant radiation therapy and 5-FU. In 1984, Moertel et al.[329] reported the results of a prospective randomized trial conducted at the Mayo Clinic with 62 patients with poor prognosis, but completely resected gastric cancers who were randomized to either surgery alone or surgery followed by radiation (37.5 Gy in 24 fractions over 4 to 5 weeks) with concurrent 5-FU. A nonstratified, prerandomization scheme was used with a 2:3 ratio favoring treatment. Ten of the thirty-nine patients refused further therapy and were observed. When analyzed by intent to treat, the adjuvant arm had statistically significant improvement in both relapse-free survival and OS (overall 5-year survival 23% versus 4%; p <0.05). When patient outcome was compared with actual treatment received (29 adjuvant treatment, 33 surgery alone), 5-year survival continued to favor the adjuvant group (20% versus 12%), but the differences were not statistically significant in view of the small patient numbers. The 10 patients who refused assignment to adjuvant treatment had more favorable prognostic findings than the other two groups of patients. When the two groups with equally poor prognostic factors were compared, the 5-year OS was 20% versus 4%, with an advantage to those receiving adjuvant radiation and 5-FU treatment. When analyzed by treatment delivered, locoregional relapse was decreased with adjuvant treatments (54% with surgery alone versus 39% with irradiation and 5-FU).

The Intergroup Trial (INT 0116) randomized patients to receive surgery alone or surgery plus postoperative 5-FU–based chemotherapy and radiation.[330] The trial included patients with stages IB–IVA nonmetastatic adenocarcinoma of the stomach or GEJ. After en bloc resection, 556 patients were randomized to either observation alone or postoperative combined-modality therapy consisting of one monthly 5-day cycle of 5-FU and leucovorin, followed by 45 Gy in 25 fractions plus concurrent 5-FU and leucovorin (4 days in week 1, 3 days in week 5) followed by two monthly 5-day cycles of 5-FU and leucovorin. Nodal metastases were present in 85% of the cases. With 5 years of median follow-up, 3-year relapse-free survival was 48% for adjuvant treatment and 31% for observation (p = 0.001); 3-year OS was 50% for treatment and 41% for observation (p = 0.005). The median OS in the surgery-only group was 27 months, compared with 36 months in the chemoradiotherapy group; the HR for death was 1.35 (95% CI = 1.09 to 1.66; p = 0.005). The hazard ratio for relapse in the surgery-only group as compared with the chemoradiotherapy group was 1.52 (95% CI = 1.23 to 1.86; p <0.001). The median duration of relapse-free survival was 30 months in the chemoradiotherapy group and 19 months in the surgery-only group. Patterns of failure were based on the site of first relapse only and were categorized as local, regional, or distant. Local recurrence occurred in 29% of the patients who relapsed in the surgery-only group and 19% of those who relapsed in the chemoradiotherapy group. Regional relapse, typically abdominal carcinomatosis, was reported in 72% of those who relapsed in the surgery-only group and 65% of those who relapsed in the chemoradiotherapy group. Extra-abdominal distant metastases were diagnosed in 18% of those who relapsed in the surgery-only group and 33% of those who relapsed in the chemoradiotherapy group. Treatment was tolerable, with three (1%) toxic deaths. Grade 3 and 4 toxicity occurred in 41% and 32% of cases, respectively. The results of this large study demonstrate a clear survival advantage for the use of postoperative chemoradiation and strongly support the integration of postoperative chemoradiation into the routine care of patients with curatively resected high-risk carcinoma of the stomach and GEJ.

The US Gastrointestinal Intergroup has recently completed a second randomized prospective trial (Cancer and Leukemia Group B 80101) in patients with completely resected high-risk gastric cancer, comparing two chemotherapy regimens given before and after 5-FU–based chemoradiation. This study examines the use of one cycle of postoperative ECF (epirubicin 50 mg/m^2, cisplatin 60 mg/m^2, and continuous infusion 5-FU 200 mg/m^2 per day for 21 days) followed by radiation therapy with concurrent

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continuous infusion 5-FU (200 mg/m^2 per day) and two additional cycles of ECF. This is compared with one cycle of postoperative 5-FU and leucovorin followed by concurrent continuous infusion 5-FU (200 mg/m^2 per day) and two additional cycles of 5-FU and leucovorin. This study was recently reported in abstract form and failed to demonstrate a survival advantage of the addition of ECF therapy to standard 5-FU and leucovorin.[331]

To address the important question of the value of postoperative radiation following D2 resection, a Korean phase 3 study comparing postoperative cisplatin/capecitabine (XP) versus postoperative XP with capecitabine and radiation was reported.[332] In this study, 458 patients were enrolled, with 228 randomly assigned to receive adjuvant chemotherapy (XP for six cycles) and 230 patients assigned to receive adjuvant chemoradiation (XPx2 → capecitabine and radiation → XPx2). Although the primary end point of improved 3-year DFS was not met ($p = 0.862$), in the subset of patients with node-positive gastric cancer ($n = 396$), adjuvant chemoradiotherapy was associated with a superior DFS (HR = 0.6865; 95% CI = 0.4735 to 0.9952; $p = 0.471$). Based on these intriguing data, the investigators have initiated a confirmatory study limited to patients with lymph node–positive resected gastric cancer (ARTIST-II).

To address the role of adjuvant chemoradiation in light of the MAGIC trial, the Dutch Colorectal Cancer Group has initiated the CRITICS trial. This study is a phase 3 prospective randomized trial that investigates whether chemoradiotherapy (45 Gy in 5 weeks with daily cisplatin and capecitabine) after preoperative chemotherapy (3 × epirubicin, cisplatin, and capecitabine) and adequate (D1+) gastrectomy leads to improved survival in comparison with postoperative chemotherapy alone (3 × epirubicin, cisplatin, and capecitabine). Further evaluating the role of adjuvant radiation therapy, a Korean phase 3 trial (the ARTIST study) is randomizing patients undergoing D2 gastrectomy to adjuvant cisplatin and capecitabine, with or without radiation therapy.

Although no phase 3 trials have tested the value of preoperative radiation plus chemotherapy for patients with gastric cancer, two phase 2 trials for patients with esophagus cancer have included either lesions of the gastric cardia or the EGJ.[333,334] In both trials, the trimodality study arm demonstrated an improvement in OS when compared with the control arm of surgery alone. The series by Walsh et al.[333] (adenocarcinoma of the esophagus or gastric cardia) demonstrated a median survival of 16 months versus 11 months, and 3-year survival of 32% versus 6% ($p = 0.01$), with the statistically significant advantage to trimodality treatment. The US GI Intergroup phase 3 trial (adenocarcinoma or squamous cell of esophagus or EGJ), which closed prematurely because of low accrual, reported a median survival of 54 months versus 22 months, and 5-year survival of 39% versus 16% ($p = 0.008$), with a significant advantage associated with the trimodality arm.[334] In addition, a recent phase 3 randomized German trial compared preoperative chemotherapy alone (5-FU, leucovorin, and cisplatin) versus the same regimen followed by low-dose radiation therapy (30 Gy) with concurrent cisplatin and etoposide in patients with adenocarcinoma of the lower esophagus or gastric cardia. Although the trial was closed early because of poor accrual (126 patients), patients receiving radiation therapy had significantly higher pathologic complete response rates (2% versus 16%; $p = 0.03$) and trend toward improved survival (3-year survival 47% versus 28%; $p = 0.07$).[335]

Preoperative chemoradiation data for patients with gastric cancer exclusively is limited to phase 2 studies from single institutions and cooperative groups. The MD Anderson Cancer Center has reported a study in which 33 patients completed a preoperative protocol that started with induction chemotherapy of 5-FU, leucovorin, and cisplatin, followed by 45 Gy of radiation therapy in 25 fractions over 5 weeks with concurrent infusional 5-FU. In 28 patients (85%), a gastrectomy was performed and D2 lymph node dissection was attempted. Pathologic complete and partial responses were found in 64% of all operated patients. These patients showed a significant longer median survival of 64 months in comparison with 13 months in patients with tumors that showed no pathologic response to preoperative chemoradiation.[336] In a study from the same institution, 41 patients with operable gastric cancer received two cycles of continuous 5-FU, paclitaxel, and cisplatin followed by 45 Gy of radiation therapy with concurrent 5-FU and paclitaxel. An R0 resection was achieved in 78% of patients; pathologic complete response was seen in 25% and pathologic partial response in 15% of patients. Pathologic response, R0 resection, and postoperative T and N stage correlated with overall and DFS.[337]

The Radiation Therapy Oncology Group (RTOG 9904) reported the results of a phase 2 study of 49 patients undergoing induction 5-FU, leucovorin, and cisplatin followed by concurrent radiation therapy, and infusional 5-FU and paclitaxel. Resection was attempted 5 to 6 weeks after chemoradiation. The pathologic complete response and R0 resection rates were 26% and 77%, respectively. At 1 year, more patients with tumors exhibiting a pathologic complete response (89%) were alive than patients with tumors having less favorable pathologic treatment response (66%). Grade 4 toxicity occurred in 21% of patients. These data appear to support a phase 3 study evaluating preoperative radiation therapy and chemotherapy versus postoperative radiation therapy and chemotherapy.[338]

TECHNICAL TREATMENT-RELATED ISSUES

Surgery

Surgery begins with careful laparoscopic staging and examination. Inspection for the presence of ascites, hepatic metastases, peritoneal seeding, disease in the pelvis (such as a "drop" metastasis), or ovarian involvement should be performed. Once distant metastases have been ruled out, depending on the location of the lesion, a bilateral subcostal incision or a midline abdominal incision can be used to gain adequate exposure to the upper abdomen. The stomach should be inspected to assess the location and extent of the primary tumor. The size and location of the primary tumor dictate the extent of gastric resection. A D2 lymphadenectomy sparing the spleen and pancreas can be done safely, and provides an excellent surgical specimen for pathologic staging, but this procedure should only be performed by or with an experienced surgeon.

The D2 subtotal gastrectomy commences with mobilization of the greater omentum from the transverse colon. After the omentum is mobilized, the anterior peritoneal leaf of the transverse mesocolon is incised along the lower border of the colon, and a plane is developed down to the head of the pancreas. The infrapyloric lymph nodes are dissected and the origin of the right gastroepiploic artery and vein are ligated. With a combination of blunt and sharp dissection, the plane of dissection continues on to the anterior surface of the pancreas, extending to the level of the common hepatic and splenic arteries. This maneuver can be tedious, but it theoretically provides additional protection against serosal spread of tumor to the local peritoneal surface. The right gastric artery is ligated. At this point, the duodenum is divided distal to the pylorus. The stomach and omentum are then reflected cephalad. The gastrohepatic ligament is divided close to the liver up to the gastroesophageal junction. Dissection is then continued along the hepatic artery toward the celiac axis. Once near the celiac axis, the lymph node–bearing tissue is dissected until the left gastric artery is visualized and can be divided at its celiac origin. The proximal peritoneal attachments of the stomach and distal esophagus can then be incised, and the proximal extent of resection is defined. For tumors of the mid- and proximal stomach, dissection of the lymph nodes along the splenic artery and splenic hilum is important. This technique is not indicated for antral tumors, given the low rate of splenic hilar nodal metastases seen with tumors in this anatomical location. The stomach is then divided 5 cm

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proximal to the tumor, which dictates the extent of gastric resection. Despite the fact that the entire blood supply of the stomach has been interrupted, a cuff of proximal stomach invariably shows good vascularization from the feeding distal esophageal arcade. When feasible, most surgeons prefer to anastomose jejunum to stomach rather than to esophagus because of the technical ease and excellent healing seen with gastrojejunal anastomosis. Reconstruction using a variety of techniques has been described and is a matter of personal choice.

Antibiotics Prophylaxis

One RCT (n = 501) tested single-dose cefazolin or ampicillin-sulbactam 30 minutes before surgery versus multiple dose regimen for 3 days postoperatively. There were no differences in surgical site infections or complication.[280,339]

Nasogastric Drainage After Gastrectomy

The Italian Total Gastrectomy Study Group reported on the largest RCT comparing total gastrectomy with Roux-en-Y with and without nasogastric tube (n = 237). There were no differences in overall morbidity, leak rate, hospital stay, and time to diet.[340] Other authors confirmed that nasogastric tube is not necessary after gastrectomy.[341–343]

Intraperitoneal Drains After Gastrectomy

As with other pathologies, two RCTs concluded that drains after gastrectomy are generally not indicated, and in certain situations can increase significantly operative morbidity.[344,345]

Reconstruction After Gastrectomy

Iivonen et al.[346] compared Roux-en-Y with and without pouch. They randomized 48 patients and found significantly less dumping syndrome and early satiety but with no differences at 15 months of follow-up. Fein et al.[347] reported on 138 patients randomized in a similar fashion; they found similar QOL at 1 year but significantly improved QOL at 3-, 4-, and 5-year follow-up. It seems that reconstruction with pouch has long-term advantages and may be recommended as the standard reconstruction.[280]

Radiation Treatment

Technique of Radiation Therapy

Idealized portals generated from patterns of failure data should be modified on the basis of the individual patient's initial extent of disease.[348,349] Based on the likely sites of locoregional failure, the gastric/tumor bed, anastomosis and gastric remnant, and regional lymphatics should be included in most patients undergoing postgastrectomy radiation.[350–353] Major nodal chains at risk include the lesser and greater curvature; celiac axis; pancreaticoduodenal, splenic, supra-pancreatic, and porta hepatis groups; and, in some, para-aortic to the level of mid-L3.

The relative risk of nodal metastases at a specific nodal location depends on both the site of origin of the primary tumor, and other factors including width and depth of invasion of the gastric wall.[349] Tumors that originate in the proximal portion of the stomach and the GEJ have a higher propensity of spread to nodes in the mediastinum and pericardial region, but a lower likelihood of involvement of nodes in the region of the gastric antrum, periduodenal area, and porta hepatis. Tumors that originate in the body of the stomach can spread to all nodal sites, but have the highest likelihood of spreading to nodes along the greater and lesser curvature near the location of the primary tumor mass. Tumors that originate in the distal stomach, in the region of the gastric antrum, have a high likelihood of spread to the periduodenal, peripancreatic, and porta hepatis nodes, whereas they have a lower likelihood of spread to the nodes near the cardia of the stomach, the periesophageal and mediastinal nodes, or to the splenic hilar nodes. Any tumor originating in the stomach has a high propensity of spread to nodes along the greater and lesser curvature, although they are most likely to spread to those sites in close anatomic proximity to the primary tumor mass. Guidelines for defining the clinical target volume for postoperative irradiation fields have been developed based on location and extent of the primary tumor (T stage), and location and extent of known nodal involvement (N stage).[349] In general, for patients with node-positive disease, there should be wide coverage of tumor bed, remaining stomach, resection margins, and nodal drainage regions. For node-negative disease, if there is a good surgical resection with pathologic evaluation of at least 15 nodes, and there are wide surgical margins proximal and distal to the primary tumor (at least 5 cm), treatment of the nodal beds is optional. Treatment of the remaining stomach should depend on a balance of the likely normal tissue morbidity and the perceived risk of local relapse in the residual stomach.

Although parallel-opposed anteroposterior/posteroanterior (AP/PA) fields are a practical arrangement for tumor bed and nodal irradiation, three-dimensional multifield techniques should be used if they can improve long-term tolerance of normal tissues. Tightly contoured fields should be designed to spare as much normal tissue as possible. Over the past decade, a shift has occurred toward more sophisticated treatment techniques that use multiple and often noncoplanar beams including three-dimensional and intensity-modulated radiation therapy. Attention has also been placed on accurate three-dimensional target delineated fields based on CT anatomy rather than only two-dimensional field design. In addition to refinements in radiation therapy target definition based on CT planning, technologic advances including study of and solutions for variability in target and normal organ location during a treatment course (day to day interfraction variability) and actual treatment delivered (intrafraction variability caused by respiration) have been undertaken. Interfraction variability in stomach location can be substantial, particularly among patients treated with neoadjuvant chemoradiation because of daily variations in gastric filling. Because of this, patients should generally be treated with an empty stomach. Intrafraction changes in target shape (deformation) and location are asymmetric and mainly from respiratory motion. Movement, particularly in the cranial-caudad dimension, frequently exceeds 1 to 1.5 cm. Image guidance, four-dimensional treatment planning, and respiratory gating have been developed to address these challenges.

More routine use of multiple field techniques should be considered when preoperative imaging exists to allow accurate reconstruction of target volumes. Single-institution data suggest that multiple field arrangements may produce less toxicity.[354] Although AP/PA fields can be weighted anteriorly to keep the spinal cord dose at acceptable levels using only parallel-opposed techniques, a four-field technique, if feasible, can spare spinal cord radiation exposure, with improved dose homogeneity. Dependent on the posterior extent of the gastric fundus, either oblique or more routine lateral portals can be used to deliver a 10- to 20-Gy component of irradiation to spare the spinal cord or kidney. When lateral fields are used, liver and kidney tolerance limits the use of lateral fields to ≤20 Gy. With the wide availability of three-dimensional treatment-planning systems, it may be possible to target more accurately the high-risk volume, and to use unconventional field arrangements to produce superior dose distributions. To accomplish this without marginal misses, it will be necessary to both carefully define and encompass the various target volumes, given that the use of oblique or noncoplanar beams could potentially exclude target volumes that would be included in AP/PA fields or nonoblique four-field techniques (AP/PA and laterals). In most patients, a portion of both kidneys are within the treatment field, but at least two-thirds to three-fourths of one kidney should be excluded beyond a dose of 20 Gy. For proximal gastric lesions, ≥50% of the left kidney is commonly within the irradiation portal, and

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the right kidney must be appropriately spared. For distal lesions with narrow or positive duodenal margins, a similar amount of right kidney often is included, and every effort must be taken to spare the left kidney from irradiation in order to maintain function. Late renal sequelae have not been encountered with these techniques, assuming normal renal function bilaterally.[355–357]

With proximal gastric lesions or lesions at the EGJ, a 3- to 5-cm margin of distal esophagus should be included. If the lesion extends through the entire gastric wall, a major portion of the left hemidiaphragm should be included. In these circumstances, blocking can decrease the volume of irradiated heart.

TREATMENT OF ADVANCED DISEASE (STAGE IV)

Treatment of Advanced Gastric Cancer: Palliative Systemic Chemotherapy

Chemotherapy Versus Best Supportive Care

The modest activity and substantial toxicity of cytotoxic chemotherapy has raised the question, Does palliative systemic therapy with available agents have clinical utility? That is, there was controversy as to whether a meaningful advantage is attained by early initiation of systemic therapy as opposed to providing best supportive care. Although this is a difficult hypothesis to test because of patient and physician preferences and biases, several random assignment trials were performed in the 1990s in patients with advanced incurable gastric cancer addressing this issue.

Wagner et al.[358] performed a meta-analysis for the Cochrane collaboration. They included three random assignment trials involving a total of 184 patients in whom the study design was to initiate systemic chemotherapy plus best supportive care or to provide best supportive care alone. Median survival and OS were evaluated (Table 46.6). Patients receiving chemotherapy as part of their treatment had better OS than those receiving best supportive care only, with an overall HR of 0.39 (95% CI = 0.28 to 0.52). The median survival was improved from 4.3 months for best supportive care to approximately 11 months for chemotherapy. Note that the median survival for patients receiving chemotherapy is consistent with several more recent trials. There was also a modest improvement in time to progression (TTP; 7 months for patients receiving chemotherapy versus 2.5 months for patients receiving best supportive care). Wagner et al.[358] concluded that the evidence supporting initiating chemotherapy for patients with advanced incurable gastric cancer was convincing.

In a fourth trial, QOL was assessed. The average quality-adjusted survival for patients undergoing chemotherapy was superior to patients receiving best supportive care (6 months versus 12 months). Importantly, in those best supportive care trials that reported 2-year survival (≥24 months), only patients undergoing chemotherapy survived for that period of time. The 2-year survival rate was 5% to 14% for patients receiving combination chemotherapy versus 0% for patients receiving best supportive care. More recently, the preliminary results of a small study testing the use of single-agent chemotherapy versus best supportive care in patients who have already received chemotherapy were reported. Previously treated patients were randomly assigned to best supportive care or to single-agent irinotecan plus best supportive care. Although the study was initially powered to require 120 patients, accrual to this type of trial was difficult and a total of only 40 patients were eventually randomized. There was a modest improvement in OS, with median survival for those receiving irinotecan of 123 days, and median survival for those with best supportive care 73 days (HR = 2.85).[359] These results are in concert with the earlier studies in previously untreated patients and indicate that systemic therapy has a modest but real and clinically meaningful effect on outcome. Many cytotoxic agents have been studied in patients with advanced gastric cancer; when used as single agents, modest activity has been identified for drugs from five different classes. More recently, targeted therapy has been tested. The following section summarizes the data for the use of systemic cytotoxic chemotherapy when given with palliative intent. An extensive discussion of older agents can be found in prior editions of this textbook.

TABLE 46.6

Chemotherapy for Advanced Gastric Cancer: Treatment Versus Best Supportive Care

Regimen	No. of Patients	Median Survival (mo)	Survival Rate (%) 1y	Survival Rate (%) 2y
FAMTX	30	10	40	6
BSC	10	3	10	0
FEMTX	17	12	—	—
BSC	19	3	—	—
ETOPLF	10	10	—	—
BSC	8	4	—	—
ELF	52	10.2	34.6	9.6
BSC	51	5	7.8	0
Irinotecan	21	123[a]	—	—
BSC	19	73[a]	—	—

F, fluorouracil; A, doxorubicin; MTX, methotrexate; BSC, best supportive care; E, epirubicin; ETOP, etoposide; L, leucovorin.
[a] Median survival in days.
Modified from Wils J. The treatment of advanced gastric cancer. *Semin Oncol* 1996;23:397.

Single-Agent Chemotherapy

For most drugs, a variety of doses and schedules have been studied. In the absence of comparative trials using the same agent with different doses and schedules, superiority of one regimen over the other cannot be assessed. Table 46.7 gives a listing of agents that have demonstrated at least modest activity in the treatment of gastric cancer and which are routinely employed as part of standard practice options. Drugs with little or no activity, especially if they were evaluated prior to 2000, are not included in this table.

5-FU is the parent fluorinated pyrimidine that has been the most extensively studied single agent in gastric cancer. An antimetabolite, the drug has been used in a variety of schedules and doses in various epithelial malignancies of gastrointestinal origin. One method involved the use of rapid intravenous injections on a weekly basis, or daily for 5 consecutive days. In gastric cancer, continuous infusion 5-FU has been used more recently. During the 1990s, in several studies, 5-FU was the control arm of a random assignment trial or was studied as a single agent (with leucovorin) in a prospective phase 2 trial. This allowed an assessment using more modern criteria of activity. The studies from the 1990s suggest overall response rates of 10% to 20%, with a median duration of response, or TTP, of approximately 4 months. As is the case in other diseases, the major toxicities reported in gastric cancer for 5-FU are mucositis, diarrhea, or mild myelosuppression. Because continuous intravenous infusion schedules can be cumbersome, oral analogues of 5-FU have been studied in gastric cancer. Three oral drugs of this class have undergone study in gastric cancer. These are tegafur and uracil (UFT), S-1 (tegafur and two modulators, 5-chloro-2,4-dihydroxypyridine and potassium oxonate), and capecitabine (Xeloda, Hoffmann-La Roche, Basel, Switzerland). The data for these agents are also shown in Table 46.7. S-1 has been most extensively studied in Japan. Although a response rate to

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TABLE 46.7

Activity of Selected Single Agents in Advanced Gastric Cancer

Drug	Response Rate (%)
Fluorinated Pyrimidines	
5-Fluorouracil	21
UFT	28
S-1	49
Capecitabine	26
Antibiotics	
Doxorubicin hydrochloride	17
Epirubicin hydrochloride	19
Heavy Metals	
Cisplatin	19
Taxanes	
Paclitaxel	17
Docetaxel	19
Camptothecans	
Irinotecan hydrochloride	23

UFT, tegafur and uracil; S-1, tegafur and two modulators, 5-chloro-2, 4-dihydroxypyridine and potassium oxonate.
From van De Velde CJH, Kelsen D, Minsky B. Gastric cancer: clinical management. In: Kelsen D, Daly JM, Kern SE, et al., eds. *Principles and Practice of Gastrointestinal Oncology*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2008, with permission.

single-agent S-1 of 44% to 54% was reported in Japanese patients, the response rate among European patients was substantially lower. Like capecitabine, S-1 is now undergoing study in combination with other agents, particularly cisplatin. UFT combines tegafur and uracil. In gastric cancer, a response rate of 28% was seen in Japanese patients. In a small European study, Okines et al.[360] reported the results of a European Organisation for Research and Treatment of Cancer (EORTC) study combining UFT and leucovorin. A 16% response rate was seen in a group of 23 patients. Capecitabine has been tested in fewer single-agent studies in gastric cancer. The data available suggest similar activity as seen with other oral fluorinated pyrimidines. Capecitabine has recently been extensively studied in combination with cisplatin or oxaliplatin (see "The REAL-2 Trial").

Platinum compounds are an important part of the treatment of gastric cancer. The parent analogue, cisplatin, was studied in the 1980s. In both previously treated and untreated patients, a response rate of approximately 15% was reported. The major toxicities for cisplatin are nausea and vomiting, peripheral neuropathy, ototoxicity, and nephropathy. The development of efficacious antiemetics has significantly improved control of nausea and vomiting. An analogue of cisplatin, carboplatin, has been less well studied in gastric cancer; it appears to have less activity in this disease, as compared to other epithelial malignancies. Most recently, oxaliplatin, a diamino cyclohexane extensively used in the treatment of colorectal cancer, was included as part of combination chemotherapy for gastric cancer. The data for combination therapy, including oxaliplatin and data from the REAL-2 trial, are shown later.

A third class of cytotoxic agents with activity in gastric cancer is the taxanes. Both paclitaxel and docetaxel have been studied as single agents in gastroesophageal cancers. Docetaxel has been more extensively studied than paclitaxel. De Cosimo et al.[361] reviewed trials in which docetaxel was used as single agent. Patients may have received prior treatment, and 262 patients were evaluable for response. The overall response rate was 19%. The major toxicities were neutropenia, alopecia, and edema. Allergic reactions were seen in about 25% of patients. The most common dosing schedule for docetaxel is 100 mg/m^2 every 3 weeks. When reported, the median TTP while on docetaxel therapy was 6 months. A schedule using lower doses given once weekly has also been studied with similar activity. On the basis of a large randomized study comparing CF to docetaxel-cisplatin–5-FU (DCF), docetaxel was approved by the US Food and Drug Administration for the treatment of advanced gastric cancer. Paclitaxel has also been studied in gastric cancer, although in smaller numbers of patients, and has a similar degree of cytotoxic activity.

A fourth class of active agent is represented by irinotecan. It has been studied both as a single agent and in combination with other cytotoxic agents. When used alone, response rates of 15% to 25% have been reported in both previously treated and untreated patients with advanced gastric cancer. Wagner et al.[358] reviewed the data for combinations, including irinotecan versus multidrug combinations not including irinotecan. They concluded that irinotecan-containing multidrug chemotherapy combinations had a modest survival benefit, which was not statistically significant, when compared with regimens not including irinotecan. The major toxicities of irinotecan are myelosuppression and diarrhea.

Anthracyclines also have activity in gastric cancer. Single-agent data from the 1960s and 1970s show a response rate for doxorubicin of 17%, and for epirubicin a similar response rate of approximately 19%. The anthracyclines have undergone more extensive study in combination chemotherapy for advanced gastric cancer.

Single-Agent Versus Combination Chemotherapy

The potential advantage of giving combination chemotherapy versus single-agent chemotherapy has been evaluated by Wagner et al.[358] in an update of their original Cochrane review. They found that combination chemotherapy had a significant survival advantage when compared to single-agent chemotherapy (HR = 0.82; 95% CI = 0.74 to 0.90). The difference in average median survival, however, was modest: 8.3 months for combination chemotherapy versus 6.7 months for single-agent chemotherapy. In the updated analysis, a test for heterogeneity was not statistically significant; they concluded that this indicated that the results of the different studies were consistent. A secondary analysis for response rate and for TTP also favored combination chemotherapy. Not surprisingly, toxicity is higher when several agents are given together, although this was not statistically significant. Treatment-related mortality was only slightly higher (1.5%) for patients receiving combination chemotherapy versus 1.1% when single-agent chemotherapy was used.

They also evaluated the role of several different combinations of cytotoxic agents, including anthracyclines as part of combination chemotherapy. In this analysis, three studies with a total of 500 patients were included. Wagner et al.[358] found that including anthracyclines in a CF combination had a modest survival advantage over CF alone (HR = 0.77; 95% CI = 0.62 to 0.95). A similar advantage to anthracyclines in combination was found when 5-FU–anthracycline combinations without cisplatin were studied. In contrast to anthracyclines, there was a more modest, albeit not statistically significant, benefit for irinotecan-containing combinations. Once again, there was a modest improvement in OS for docetaxel-containing regimens, but this did not reach statistical significance. The response rate as a secondary objective was 36% for docetaxel-containing regimens versus 31% for nondocetaxel-containing regimens (not statistically significant). Oral fluoropyrimidines when compared to intravenous fluoropyrimidine therapy also showed no significant difference in median OS. The meta-analysis is in concert with the results of the REAL-2 trial, which indicated noninferiority for oral capecitabine when compared to intravenous 5-FU. Similarly, oxaliplatin regimens were compared to cisplatin-containing regimens with modest superiority to oxaliplatin.

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In summary, there are five classes of cytotoxic chemotherapy agents in which single agents have modest activity in gastric cancer. The response rates range from 10% to 25%, and the median duration of response is relatively short (4 to 6 months). As a result of the single-agent trials, 5-FU or capecitabine (or other oral fluoropyrimidines), cisplatin or oxaliplatin, docetaxel, and less commonly, paclitaxel, epirubicin, and irinotecan are the major components of conventional combination cytotoxic systemic chemotherapy regimens.

Like other malignancies, multidrug regimens using agents that have single-agent activity have been extensively studied in gastric cancer. This section will focus on phase 3 random assignment trials. For some combinations, only phase 2 data are available. The recent Cochrane review summarizing a comparison of different regimens including three-drug versus two-drug combinations has already been discussed.[358]

Cisplatin-Fluorouracil. One of the most widely used combination chemotherapy regimens in upper gastrointestinal tract malignancies, including gastric cancer, is the two-drug combination of CF. Although this regimen has been used for several decades, with a variety of doses and schedules employed, since 2000, several phase 3 random assignment trials have been performed in which CF was the control arm. This allowed an opportunity for an evaluation of the efficacy of this combination, in patients with advanced incurable gastric cancer, both in terms of response rate, PFS, and OS, using currently accepted criteria for efficacy and toxicity of treatment. Table 46.8 shows the data from six studies in which CF was the control arm.[362] The doses of cisplatin used were 80 to 100 mg/m^2 per course. 5-FU was given as a continuous 24-hour infusion from days 1 through 5 at a dose of 800 to 1,000 mg/m^2 per day. Cycles were usually given on an every 28-day basis. Efficacy outcomes were consistent across these trials. Response rates, PFS, and OS were quite similar. Major objective tumor regression was reported in 20% to 30% of patients; complete clinical remission was very uncommon, however. The median TTP or PFS, depending on the study, ranged from 3.7 months to 4.1 months, with median survival ranging from 7.2 months to 8.6 months. Two-year survival was between 7% and 10%. CF was compared to a variety of other agents in these trials.

Vanhoefer et al.,[363] reporting for EORTC, compared CF to methotrexate, 5-FU, and doxorubicin (FAMTX); a third group of patients received etoposide, leucovorin, and 5-FU combination. There was no significant difference in outcome among the three arms. A Japanese study (JC 09205) also had three systemic therapy arms.[364] 5-FU was compared to CF, and to a third arm of uracil/tegafur plus mitomycin. In this study, there was no advantage for the two-drug combination of CF over 5-FU alone. The final results of the TAX315 trial have recently been published.[365] The details of this study are described later. An advantage was seen for the DCF arm. The CF control arm results were similar to those seen in the earlier trials previously described. The two-drug combination of 5-FU plus irinotecan was compared to CF by Dank et al.[366] CF was equivalent to irinotecan plus 5-FU. Kang et al.[367] reported the results of the RCT comparison between CF versus cisplatin-capecitabine. This study was designed as a noninferiority trial with the hypothesis that capecitabine-cisplatin was not inferior to CF. The end point was PFS. The dose of cisplatin was slightly lower than in the studies described earlier (80 mg/m^2). However, therapy was given on every-3-week basis; 316 patients were treated. The median PFS was 5 months for CF; median survival was 9.3 months. Ajani et al.[368] reported the results of the FLAGS trial, which is described in more detail later. In this study involving 1,029 eligible patients, the control arm of CF had a median OS of 7.9 months.

In summary, the random assignment trials discussed previously indicate consistent data for efficacy (and toxicity) for the two-drug combination CF. The Japanese study raises the question as to whether there is a substantial clinical advantage to CF over

TABLE 46.8

Combination Chemotherapy in Advanced Gastric Cancer: Cisplatin-Fluorouracil-Containing Regimens Used as the Control Arm in Random Assignment Trials

Study (Ref.)	Drug	Dose (mg/ml)	Schedule (d)	No. of Patients	RR (%)	Median TTP/PFS (mo)	Median Survival (mo)	Two-y Survival (%)
EORTC[363]	C	100	1	127	20	4.1	7.2	~10
	F	1,000	1–5					
JCOG[364]	C	20	1–5	105	36	7.3	3.9	7
	F	800	1–5					
Dank et al.[366]	C	100	1	163	26	4.2	8.7	~10
	F	1,000	1–5					
TAX325[365]	C	100	1	224	25	3.7	8.6	9
	F	1,000	1–5					
FLAGS[368]	C	100	1	508	32	5.5	7.9	~10
	F	1,000	1–5					
Kang et al.[367]	C	80	1	156	32	5.5	9.3	~10
	F	800	1–5					
REAL-2[360,362,374]	E	50	1	289	41	6.2	9.9	~15
	C	60	1					
	F	200	Daily					

RR, recovery rate; TTP, time to progression; PFS, progression-free survival; EORTC, European Organisation for Research and Treatment of Cancer; C, cisplatin; F, fluorouracil; JCOG, Japan Clinical Oncology Group; E, epirubicin; FLAGS, Cisplatin/S-1 With Cisplatin/Infusional Fluorouracil in Advanced Gastric or Gastroesophageal Adenocarcinoma Study; REAL, Randomized Trial of EOC +/− Panitumumab for Advanced and Locally Advanced Esophagogastric Cancer.
Modified from van De Velde CJH, Kelsen D, Minsky B. Gastric cancer: clinical management. In: Kelsen D, Daly JM, Kern SE, et al., eds. *Principles and Practice of Gastrointestinal Oncology*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2008, with permission.

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5-FU alone, but the meta-analysis performed by Wagner et al.[358] supports the use of combination over single-agent chemotherapy. Although still commonly used as a conventional standard of practice palliative treatment, the recent demonstration of modest superiority when docetaxel is added to CF (assuming that a more well-tolerated regimen using the three agents can be developed) as well as the noncomparative data using ECF, which is discussed later, suggest that CF may not be the most effective option for therapy in patients with advanced gastric cancer. The slight advantage in longer-term survival (2-year survival) in the TAX325 and in the irinotecan–5-FU–leucovorin (FOLFIRI) studies of 15% to 20%, as compared to 15% to 20% for ECF, suggests that at least some patients may have longer-term survival with newer regimens.

Although type and incidence of treatment-related toxicity is consistent across most CF trials and is generally tolerable, it can be severe on occasion. For example, in the EORTC trial, grade 3 or 4 neutropenia was seen in approximately one-third of patients; one-quarter of patients had grade 3 or 4 nausea or vomiting. Similarly, in the more recent TAX325 trial, overall grade 3 or 4 toxicity was seen in 75% of patients receiving CF; in the FLAGS trial, treatment-related mortality occurred in 4.9% of patients receiving CF. Some toxicity may be ameliorated by improved supportive care. For example, newer antiemetics such as aprepitant should improve control of severe nausea and vomiting. More widespread use of supportive cytokine agents may decrease the incidence of neutropenic fever. Nonetheless, it should be recognized that CF, using the doses and schedules described previously, is associated with substantial toxicity in some patients.

The use of oral fluoropyrimidines in place of intravenous 5-FU has been studied in several phase 3 trials, including that of Kang et al.[367] described earlier, the REAL-2 trial, and the FLAGS trial comparing CF to cisplatin–S-1. In FLAGS trial, 1,029 patients received either cisplatin 100 mg/m^2 and 5-FU 1,000 mg/m^2 as a continuous 5-day infusion or a slightly lower dose of cisplatin plus oral S-1.[368] Median OS was 8.6 months for patients receiving cisplatin plus S-1 versus 7.9 months in the CF arm, with less toxicity for the cisplatin–S-1 combination. These three trials indicate that oral fluoropyrimidine when given with a platinum compound is not inferior to intravenous 5-FU plus cisplatin.

Docetaxel, Cisplatin, and Fluorouracil. Van Cutsem et al.[365] have reported the final results of a large-scale random assignment trial comparing the DCF combination to CF (the TAX325 trial). Previously untreated patients with advanced gastric cancer received either DCF (221 analyzable patients) or CF using the doses and schedules previously described (224 patients). The primary end point of the study was TTP and was powered to detect an increase in median TTP from 4 to 6 months. The two arms of the study were well balanced for prognostic factors, including weight loss, performance status, and extent of disease. The median TTP was 3.7 months for patients receiving CF and 5.6 months for those receiving DCF (HR = 1.47; $p = 0.0004$). As a secondary end point, survival was also modestly increased from 8.6 months for CF to 9.2 months for DCF. The 2-year survival rate, however, was increased greater than two-fold in the DCF treatment arm (2-year OS: 8.8% for CF and 18.4% for DCF). Another measure of efficacy favoring DCF was tumor response to treatment (37% for DCF and 25% for CF). Although this study indicated an advantage to the three-drug combination of DCF, toxicity was also increased and was very substantial. Eighty-one percent of all patients receiving DCF had at least one grade 3 or 4 nonhematologic toxicity, as well as substantially more hematologic toxicity. Of the patients receiving CF, 14% had neutropenic fever, as did 30% of patients receiving DCF. However, there was no difference in the treatment-related mortality rate for the two arms. This study led to the recent approval of docetaxel by the US Food and Drug Administration for the treatment of gastric cancer when given in association with CF.

Like epirubicin, docetaxel, when added to CF, has a modest improvement in efficacy. The very substantial toxicity seen with the DCF regimen, however, has led to concerns regarding its general use. A number of studies have been performed using modifications of DCF to develop a more tolerable regimen. Several strategies have been pursued, most of which involve using somewhat lower doses of docetaxel and 5-FU, or modifications in the schedule as to duration of 5-FU infusion or timing of the cisplatin dose. The preliminary results of a phase 2 trial comparing one of these modified DCF regimes to the original DCF schedule indicate that modifications of the treatment schedule may decrease toxicity while maintaining treatment efficacy.[369]

Irinotecan Plus Fluorouracil-Leucovorin. A three-drug combination of FOLFIRI has been studied extensively in metastatic colorectal cancer. A random-assignment phase 2 study comparing FOLFIRI with cisplatin-irinotecan indicated a potential advantage for the FOLFIRI-type regimen.[370] Therefore, a definitive phase 3 trial was performed with CF as the control arm.[366] A total of 170 patients received irinotecan–5-FU) and 163 received CF. The primary end point was TTP. The analysis allowed for a noninferiority comparison between the two arms. The study was reasonably well balanced for the usual prognostic indicators; approximately 20% of patients had EGJ tumors. There was no significant difference in the major objective response rate (32% for irinotecan–5-FU and 26% for CF) nor in median TTP (5 months for irinotecan–5-FU and 4.2 months for CF). Overall median survival was also similar between groups (9 months for irinotecan–5-FU and 8.7 months for CF). Time to treatment failure was 4 months versus 3.4 months for irinotecan–5-FU and CF, respectively ($p = 0.018$). Irinotecan–5-FU was better in terms of toxic deaths (0.6% versus 3%), discontinuation for toxicity (10% versus 22%), neutropenia, thrombocytopenia, and stomatitis but not diarrhea than CF. The investigator's final conclusion was that irinotecan–5-FU was not inferior to CF and was somewhat less toxic.

Epirubicin, Cisplatin, and Fluorouracil. English investigators have extensively studied the three-drug combination ECF. Two random-assignment phase 3 trials have compared the ECF with a noncisplatin-containing combination (FAMTX) or with a mitomycin-cisplatin–5-FU (MCF) combination.[371] In the first study, ECF was more effective than FAMTX both in terms of response rate and median OS (8.7 months versus 6.1 months). Two-year survival was also superior for the ECF combination (14% versus 5%). In the second study, Ross et al.[371] compared ECF with MCF. In this larger study, 574 patients were treated. The primary end point was 1-year survival. The overall objective response rates were similar between the two arms (ECF 50% and MCF 55%). Toxicity was tolerable, although myelosuppression was greater for the experimental MCF arm. There was a slightly improved median duration of survival for ECF (9.4 months versus 8.7 months) and for 1-year survival (40% for ECF and 32% for MCF). There was no significant difference in 2-year survival, which was approximately 15% for both arms. Several studies have demonstrated that a small percentage of patients with advanced unresectable gastric cancer actually survive 2 years. Data for the ECF regimen as the control arm of the REAL-2 trial are discussed later.

Cisplatin Plus Irinotecan. Cisplatin is a commonly used agent in gastric cancer, and irinotecan has been combined with this drug as well as with other agents. In single-arm phase 2 studies, response rates were encouraging and toxicity was tolerable with irinotecan-cisplatin. This observation led to a somewhat larger random-assignment phase 2 trial comparing irinotecan-cisplatin with the irinotecan–5-FU regimen previously described.[370] Sixty-two patients received irinotecan–5-FU and 61 received irinotecan-cisplatin. The dose schedule used for the irinotecan-cisplatin arm was higher than that from earlier irinotecan-cisplatin regimens. In this study, the response rate was higher for irinotecan–5-FU than for irinotecan-cisplatin, as was the TTP. Although irinotecan-cisplatin in the dose and schedule used in the random-assignment

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phase 2 trial previously described was less effective than irinotecan–5-FU, other investigators have pursued this regimen using different schedules. These studies have been performed in patients with esophageal, gastroesophageal, and gastric cancers. One irinotecan-cisplatin regimen was used with bevacizumab.[372]

Fluorouracil-Leucovorin-Oxaliplatin. As is the case for irinotecan-containing regimens, oxaliplatin plus 5-FU is a standard practice option for patients with both metastatic and locally advanced colon cancer. In part because of this data, 5-FU–leucovorin-oxaliplatin (FOLFOX) regimens have also been studied in gastric cancer. The toxicity spectrum is similar to that seen in patients with colorectal cancer, with the dose-limiting toxicity of peripheral neuropathy (oxaliplatin). Myelosuppression, mucositis, and diarrhea typical for 5-FU regimens were noted as well. Several FOLFOX phase 2 studies have now been reported in gastric cancer. Overall response rates of approximately 50% were observed, with median TTP of 5 to 6 months and median OS ranging from 10 to 12 months.[373]

The REAL-2 Trial

Partly on the basis of these studies, a phase 3 trial comparing an oxaliplatin-based regimen with cisplatin-containing combinations was performed. Cunningham et al.[374] in the REAL-2 trial studied 1,002 patients who were randomized to one of four treatment groups: a control arm of ECF and three investigational arms. The central question in this study was: Can capecitabine be substituted for 5-FU and/or oxaliplatin substituted for cisplatin. The four arms were ECF, epirubicin-oxaliplatin–5-FU, epirubicin-cisplatin-capecitabine, and epirubicin-oxaliplatin-capecitabine (EOX). The four regimens are shown in Table 46.9. Patients were stratified for performance status and extent of disease. The primary end point was in OS. The study was powered to show noninferiority for capecitabine compared with 5-FU and oxaliplatin compared with cisplatin. There were approximately 250 patients per arm. The study design was a two-by-two comparison. A total of 40% of patients had primary gastric cancer, and the remainder had either EGJ or esophageal cancers, with 10% of patients having squamous cell cancer of the esophagus. There was no difference in median OS between the arms (ECF 9.9 months, epirubicin-oxaliplatin–5-FU 9.3 months, epirubicin-cisplatin-capecitabine 9.9 months, and EOX 11.2 months). The 1-year OS was also similar and ranged from 38% to 47%, the best outcome evident with EOX and the lowest with the control arm of ECF. The authors concluded the oxaliplatin could be substituted for cisplatin, and capecitabine could be substituted for 5-FU in the palliative setting.

TABLE 46.9

REAL-2 Regimens

Drug	Dose (mg/m^2)	Day(s)	Week(s)[a]
ECF			
Epirubicin	50 mg/m^2 IV	1	Every 3 wk
Cisplatin	60 mg/m^2 IV	1	
PVI 5-FU	200 mg/m^2/d[b]	1	
EOF			
Epirubicin	50 mg/m^2 IV	1	Every 3 wk
Oxaliplatin	130 mg/m^2 IV	1	
PVI 5-FU	200 mg/m^2/d[b]	1	
ECX			
Epirubicin	50 mg/m^2 IV	1	Every 3 wk
Cisplatin	60 mg/m^2 IV	1	
Capecitabine	625 mg/m^2/BID	1	
EOX			
Epirubicin	50 mg/m^2 IV	1	Every 3 wk
Oxaliplatin	130 mg/m^2 IV	1	
Capecitabine	625 mg/m^2/BID	1	

REAL, Randomized Trial of EOC +/− Panitumumab for Advanced and Locally Advanced Esophagogastric Cancer; ECF, epirubicin-cisplatin-fluorouracil; PVI, protracted venous-infusion; 5-FU, 5-fluorouracil; EOF, epirubicin-oxaliplatin-5-FU; IV, intravenously; ECX, epirubicin-cisplatin-capecitabine; BID, twice a day; EOX, epirubicin-oxaliplatin-capecitabine.
[a] Planned treatment duration 24 weeks (eight cycles).
[b] PVI 5-FU delivered by central venous access catheter.
Modified from Cunningham D, Okines AF, Ashley S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008;358:36.

Al-Batran et al.[375] reported the results of a trial comparing a FOLFOX regimen with 5-FU–leucovorin-cisplatin (FLP). A modified FOLFOX-6 schedule was used for the experimental arm. The FLP regimen used slightly lower doses of 5-FU and cisplatin (50 mg/m^2) every 2 weeks. The study was powered for superiority of FOLFOX over FLP. A total of 220 patients were randomized between the two arms. There was no significant difference in TTP ($p = 0.08$) and OS (10.7 fluorouracil 2,600 mg/m^2 via 24-hour infusion, leucovorin 200 mg/m^2, and oxaliplatin 85 mg/m^2 [FLO] every 2 weeks versus 8.8 [FLP] months). Although this study did not demonstrate superiority for oxaliplatin-containing regimens, it does support the results of the REAL-2 study for noninferiority comparing oxaliplatin and cisplatin. The FOLFOX regimen was slightly less toxic.

Finally, Kang et al.[367] compared XP with CF. A total of 160 patients received XP and 156 patients received CF. The XP arm was not inferior, with a median PFS of 5.6 months versus 5 months for CF. OS was 10.5 months versus 9.3 months for XP versus CF (HR = 0.85; 95% CI = 0.64 to 1.13; $p = 0.008$ versus noninferiority margin of 1.25). The authors concluded that XP can be considered an effective alternative to CF.

It is of note that FOLFOX, FOLFIRI, and capecitabine-containing regimens are widely used in colorectal cancer. In metastatic colorectal cancer, the median TTP using these regimens is approximately 7 to 8 months and the median survival (even without the use of bevacizumab) is 20 to 24 months. The 1-year survival for patients with stage IV unresectable colon cancer is approximately 70%, and, using these regimens, 2-year survival approaches 40%. As shown earlier, the same regimens used in patients with gastric or EGJ tumors result in substantially shorter times to progression and significantly shorter median survivals. There are more classes of active cytotoxic agents with demonstrated activity in EGJ than there are for colorectal cancer. In upper gastrointestinal tract malignancies, oxaliplatin, cisplatin, 5-FU, irinotecan, capecitabine, taxane, and anthracyclines have at least modest single-agent activity, whereas the taxanes and anthracyclines are not active in colorectal cancer. These differences in efficacy outcomes suggest biologic differences between these malignancies, despite the histologic similarities (e.g., "intestinal-type" gastric cancers).

As is the case for other solid epithelieal malignancies, an important area of investigation is the development of better preclinical models, such as murine models, and the identification of predictive and prognostic biomarkers, which may well be different between gastrointestinal tumors arising in the upper and lower gastrointestinal tract. On the other hand, using targeted therapies, predictive markers may be the same in different cancers; for example, overexpression or amplification of *HER2* is a predictive marker for the use of the monoclonal antibody trastuzumab in both breast and now gastric cancers. It is also possible that the use of another cytotoxic treatment regimen (second-line treatment) after progression of disease on the first treatment regimen in gastroesophageal cancers would lead to a similar outcome as seen in colorectal cancers. For example, in the REAL-2 trial, only 15% of patients received additional therapy at the time of progression of disease. The irinotecan versus best supportive care study described previously suggests that at least some patients will have a modest survival benefit to second-line treatment.

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Second-Line Therapy

Despite numerous chemotherapy options, the majority of patients who progress on first-line therapy are currently not treated with second-line chemotherapy in the West. In several series, only 20% to 50% of patients received second-line treatment.[376,377] Patients with gastric cancer often have numerous comorbidities and complications of their malignancy (i.e., failure to thrive with significant protein-calorie losses, peritoneal carcinomatosis with limited bowel function) that preclude the safe administration of second-line therapy. Alternatively, as many as 70% of patients from Japan and other parts of Asia receive second-line therapy. Recently, there have been two random assignment studies that demonstrate the benefits of second-line therapy.[378,379]

In one study, previously treated patients were randomly assigned to best supportive care or to single-agent irinotecan plus best supportive care. Although the study was initially powered to require 120 patients, accrual to this type of trial was difficult and a total of only 40 patients were eventually randomized. Despite the small sample size, the investigators observed a significant improvement in the HR for death (HR = 0.48) with the administration of irinotecan ($p = 0.012$).[359] In a more recent and larger Korean study, 201patients were randomized to second-line chemotherapy (either irinotecan or docetaxel) after progression on CF therapy. These investigators confirm an improvement in median OS with chemotherapy from 3.8 months with best supportive care alone to 5.1 months with the addition of chemotherapy.[379] Together, these studies definitely establish that patients with metastatic gastric cancer who have maintained their performance status should be considered for second-line palliative chemotherapy as a standard of practice.

A random assignment study was conducted in patients with advanced gastric cancer comparing paclitaxel and irinotecan in the refractory setting.[380] In this study, 223 patients were randomly assigned to either cytotoxic drug, with no difference in OS observed (median OS 9.5 months with paclitaxel and 8.4 months with irinotecan; HR = 1.13; $p = 0.38$).

Targeted Therapy

The Epidermal Growth Factor Receptor Superfamily: Monoclonal Antibodies

Trastuzumab. Overexpression or amplification of *HER2* (*EGFR2*) occurs in approximately 20% of patients with gastric cancer; it varies with the subtype. A phase 3 study of trastuzumab plus chemotherapy versus chemotherapy alone was performed in patients with gastric cancer overexpressing *HER2*. The preliminary results of the ToGA trial have been recently reported.[381] Among 3,807 patients, 594 patients had *HER2*-positive gastric cancer. They were randomized to receive either CF or XP given every 3 weeks for six cycles, or the same chemotherapy plus trastuzumab. The median OS was 13.5 months for patients receiving trastuzumab plus chemotherapy versus 11.1 months for those receiving chemotherapy alone (HR = 0.74; $p = 0.0048$). The response rate was 47% for patients receiving trastuzumab plus chemotherapy versus 35% for those receiving chemotherapy alone. There was no significant difference in toxicity between treatment arms. Trastuzumab has been approved in Europe for *HER2*-positive gastric cancer. The ToGA trial used a *HER2* scoring system similar to that used in breast cancer. *HER2* was more likely to be positive in patients with EGJ tumors than in more distal tumors (33% versus 20%); patients with diffuse gastric cancer were much less likely to have an *HER2*-positive (6%) tumor.[382]

Cetuximab and Panitumumab. Cetuximab is an antibody against epidermal growth factor receptors. In a trial combining cetuximab plus weekly infusions of oxaliplatin and 5-FU, and DL-folinic acid, 46 patients with advanced gastric cancer were treated. Toxicity was tolerable; the response rate was 56%; however, OS was 9.5 months. K-Ras mutations were rare.[383]

The Epidermal Growth Factor Receptor Superfamily: Tyrosine Kinase Inhibitors

Lapatinib. Lapatinib is the first dual inhibitor of HER1 (EGFR1) and HER2 (EGFR2). Two phase 2 trials have evaluated lapatinib monotherapy in patients with advanced gastric cancer. In one study, 3 of 46 patients had partial responses. In the second study, 21 patients with EGJ adenocarcinomas were treated without objective responses.

Gefitnib and Erlotinib. Both are epidermal growth factor receptor tyrosine kinase inhibitors. In a large study, a 9% response rate was seen for EGJ tumors versus no responses among patients with gastric cancer; other studies have failed to demonstrate activity even in EGJ tumors.

The Vascular Endothelial Growth Factor Superfamily: Monoclonal Antibodies

Bevacizumab. Bevacizumab is a humanized monoclonal antibody that binds the vascular endothelial growth factor ligand (VEGF-A). In gastric cancer, Shah et al.[372] reported on combining cisplatin plus irinotecan with bevacizumab (phase 2). Among 47 patients, the median TTP was 9.9 months. A second phase 2 study evaluating bevacizumab with DCF also showed promising activity, with median PFS of 12 months and median OS of 17 months.[384] This trial demonstrated potential efficacy with acceptable toxicity; follow-up phase 2 trials also demonstrated acceptable toxicity.[385] The AVAGAST multinational phase 3 trial comparing bevacizumab plus CP versus CP alone has now completed accrual.[386,387] Results have been reported.[388]

In this phase 3 study, 774 patients were randomly assigned to XP ($n = 387$) or XP/bevacizumab ($n = 387$). The study did not meet the primary end point of improving OS (12.1 months with XP/bevacizuamb versus 10.1 months with XP; $p = 0.1002$), but did demonstrate improvement in PFS (6.7 months versus 5.3 months; $p = 0.0037$) and overall response rates (46.0% versus 37.4%; $p = 0.0315$) with XP/bevacizumab versus XP alone, respectively.[386,387] In this study, there was distinct geographic variation in which patients enrolled from Asia appeared not to have significant benefit from the addition of bevacizumab. These results support the concept of significant worldwide disease heterogeneity.

A biomarker evaluation was prospectively performed from the AVAGAST study, in which plasma samples were available from 92% of the study population and tissue samples were available from 94% of the study population.[389] In this analysis, baseline plasma VEGF-A levels and tumor neuropilin-1 expression were identified as potential predictors of bevacizumab efficacy. Specifically, patients with high baseline plasma VEGF-A appeared to benefit from bevacizumab therapy (HR = 0.72; 95% CI = 0.57 to 0.93), and similarly, patients with low baseline expression of neuropilin-1 also showed a trend toward improved OS with bevacizumab (HR = 0.75; 95% CI = 0.59 to 0.97). These data, if validated, may provide important insights pertaining to the geographic heterogeneity observed with this international phase 3 study, and importantly, may identify a population of patients for whom bevacizumab would have substantial efficacy when combined with chemotherapy.

The Vascular Endothelial Growth Factor Superfamily: Tyrosine Kinase Inhibitors

Sunitinib. Sunitinib is an oral inhibitor of VEGF receptor [VEGFR]-1, -2, -3, and PDGFR-α, -β, and c-kit. Bang et al.[389] reported on a phase 2 trial of sunitinib as second-line treatment for

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advanced gastric cancer. Response rate, PFS, and OS were 2 of 72 patients, 11.1 weeks, and 47.7 weeks, respectively. Sorafenib is another multityrosine kinase inhibitor (VEGFR-2, -3; platelet-derived growth factor receptor–β; Flt-3; Raf-1; and c-kit). The ECOG5203, a phase 2 trial investigating docetaxel plus cisplatin plus sorafenib in gastric cancer, suggested clinical efficacy (response rate = 39%; PFS = 5.8 months; OS = 15.9 months).[390]

Recently, a random assignment phase 2 study of apatinib, a tyrosine kinase inhibitor that selectively inhibits VEGFR2, appears to be active in advanced gastric cancer.[391] In this study, 144 patients were randomly assigned to placebo or two different doses of apatinib. Patients assigned to apatinib had a statistically significant improved OS (4.83 and 4.27 months in the apatinib arms versus 2.5 months in the placebo; $p = 0.0017$), with nine patients demonstrating a radiographic partial response.

In addition, a second study has demonstrated efficacy of VEGFR2 inhibition as monotherapy in gastric cancer. Ramucirumab (IMC-1121B) is a fully human IgG1 monoclonal antibody targeting VEGFR-2. The Regard study was a placebo-controlled, double blind, phase 3 international trial conducted in the second-line setting in patients with metastatic gastric or EGJ adenocarcinoma. Median OS was 5.2 months for ramucirumab and 3.8 months for placebo (HR = 0.776; 95% CI = 0.603 to 0.998; $p = 0.0473$). The significance of this study is that it provides a proof-of-principal that antiangiogenic therapy does have activity in gastroesophageal malignancies. The Regard study supports the concept that subtypes of gastric cancer exist and may be differentially sensitive to antiangiogenic therapy.[392]

Inhibition of Mammalian Target of Rapamycin (Protein Kinase)

Everolimus. An oral inhibitor of the mammalian target of rapamycin has shown activity against gastric cancer in preclinical phase 1 studies.[393,394] Doi et al.[394] reported on a phase 2 trial testing everolimus in metastatic gastric cancer. In 53 patients, the disease control rate (complete response rate plus partial response plus stable disease) was 56%, and the median PFS and OS were 2.7 and 10.1 months, respectively. Based on these encouraging results, a phase 3 study was performed comparing everolimus to best supportive care.[395] In this study, 656 patients were randomized in a 2:1 fashion to everolimus versus placebo. Median OS was similar in both arms, 5.4 months versus 3.2 months (HR = 0.9; 95% CI = 0.75 to 1.08; $p = 0.12$).

In summary, new agents targeting dysregulated cancer pathways are now undergoing study in gastric cancer. At the present time, trastuzumab remains the only drug of this type that has demonstrated efficacy, in combination with cytotoxic chemotherapy, in gastric cancer.

Predictive Markers and Early Assessment of Response in Gastric and Gastroesophageal Tumors

The recognition that several different classes of cytotoxic anticancer agents and targeted pathway agents have activity in subgroups of patients suggests the possibility that predictive markers or a gene signature might allow "customized" precision cancer care that will spare patients from unnecessary toxicity from ineffective therapy, such as testing for *HER2* identifies patients who could benefit from trastuzumab. Molecular markers that might indicate resistance or sensitivity to CF are reviewed elsewhere in this book.[396] Ooi et al.[396] and other investigators[397–399] have used gene expression arrays to identify pathways and gene signatures to predicting clinical prognosis. Ott et al.[77] reported that a drop in SUV of 35% after neoadjuvant chemotherapy was associated with significant pathologic response to systemic treatment. Similar findings were reported by Shah et al.[400] and Weber.[401] Overall, PET may allow early identification of patients responding to systemic therapy.

SURGERY IN TREATMENT OF METASTATIC GASTRIC CANCER

Given the recent improvements in systemic therapy for gastric cancer, the question whether resection of limited metastases from gastric cancer can provide survival benefit remains unanswered. To ask this question in a scientific manner, the surgery branch of the National Institutes of Health/National Cancer Institute is currently accruing patients to a prospective RCT comparing gastrectomy, metastasectomy plus systemic therapy, versus systemic therapy alone (the GYMSSA Trial, clinicaltrials.gov no. NCT00941655).[402]

The GYMSSA trial randomized patients with metastatic gastric cancer to gastrectomy, cytoreductive surgery (CRS)/HIPEC plus Folfoxiri (GYMS arm) versus Folfoxiri alone (SA arm) to study OS. All patients underwent comprehensive staging including laparoscopy. To date, the study accrued 16 evaluable patients. Seven of nine patients in the multimodality GYMS arm achieved complete cytoreduction, with median follow-up of 23 months. Median OS was 12 months in the GYMS arm and 10.2 months in the SA arm; 1- and 2-year OS was 44% and 22% versus 0% and 0%, respectively. Two patients in the GYMS arm lived beyond 23 months, and one up to 12 months. No patient in the SA arm lived longer than 12 months.

Kerkar et al.[401,402] reviewed the published data reporting on liver resection for gastric cancer; 19 studies reported on 436 patients. The majority of the patients had synchronous isolated liver gastric metastases. Overall, the 1-, 3-, and 5-year survival rates were 62%, 30%, and 27%, respectively; 13% (48/358) were alive at 5 years, and in studies with >10 years of follow-up, 4% (48/358) survived for >10 years.[402]

Standard of care for patients with pulmonary gastric metastases is chemotherapy with a median survival of 6 months.[403] Kemp et al.[403] reviewed the published data reporting on lung resections for gastric cancer; 21 studies reported on 43 patients. Eighty-two percent of patients (34/43) had a solitary lesion. At a median follow-up of 23 months, 15 of 43 (35%) patients had no evidence of disease. The overall 5-year survival was 33%.

Gastric carcinomatosis occurs in 5% to 50% of patients undergoing surgery with curative intent.[404–410] The median survival for such patients is 1.5 months to 3.1 months.[404,411–413] Overall data are limited; however, several investigators reported on CRS plus HIPEC for gastric carcinomatosis; the median OS ranged from 6 to 21 months, and 5-year survival ranged from 6% to 16% with operative mortality of 2% to 7% mortality. In patients with optimal cytoreduction-CCR-0/1 (no macroscopic or disease <5 mm), the 5-year survival was 16% to 30%. Complete cytoreduction was possible in only 44% to 51% of the patients.[309,414–418] In 2008, the Fifth International Workshop on Peritoneal Surface Malignancy indicated that peritonectomy, intraoperative, and early postoperative HIPEC potentially can be a powerful therapy against gastric cancer peritoneal carcinomatosis.[419–424]

Bidirectional chemotherapy utilizing intraperitoneal and systemic induction chemotherapy prior to CRS and HIPEC has been studied (retrospectively) in patients with peritoneal carcinomatosis of gastric origin undergoing treatment in a specialized peritoneal surface malignancy unit in Japan. A recent study of 194 patients with gastric carcinomatosis treated initially and responsive (response rate 78%) to intraperitoneal docetaxel (20 mg/m^2) and cisplatin (30 mg/m^2) followed by four cycles of oral S-1 (60 mg/m^2), followed by CRS/HIPEC reported median OS of 16 months and 1-, 2-, and 5-year survival of 66%, 32%, and 11%, respectively.[425] Operative morbidity and moratlity were 24% and 4%, respectively. Response to bidirectional intraperitoneal and systemic chemotherapy, low tumor burden (peritoneal cancer index ≤6) and completeness of cytoreduction (CCR0/1) were independently associated with improved OS on multivariate analysis.

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Surgery for Palliation

Because survival for patients with advanced gastric cancer is poor, any proposed operation could have a good chance of providing sustained symptomatic relief while minimizing the attendant morbidity and need for prolonged hospitalization. Ekbom and Gleysteen[426] have reviewed the results of palliative resection versus intestinal bypass (gastrojejunostomy) in 75 patients with advanced gastric cancer. The most frequent symptoms for which patients underwent operation included pain, hemorrhage, nausea, dysphasia, or obstruction. Operative mortality was 25% for gastrojejunostomy, 20% for palliative partial or subtotal gastrectomy, and 27% for total or proximal palliative gastrectomy. The most common and often fatal complication was anastomotic leak. After gastrojejunostomy, 80% of patients had relief of symptoms for a mean of 5.9 months compared with palliative resection, which provided relief of symptoms in 88% of patients for a mean of 14.6 months. Although the duration of palliation was significantly longer after resection ($p < 0.01$), the selection criteria for resection versus bypass were not controlled, and some bias against performing a palliative resection in high-risk patients with more advanced disease may have occurred. Meijer et al.[427] also reported on a retrospective analysis of 51 patients undergoing either palliative intestinal bypass or resection. In 20 of 26 patients (77%) undergoing resection, palliation was considered moderate to good with a mean survival of 9.5 months. After gastroenterostomy, some palliation was noted in 8 of 25 patients (30%), and survival was 4.2 months. Butler et al.[428] have presented the results of total gastrectomy for palliation in 27 patients with advanced gastric cancer. Operative mortality was only 4%, whereas morbidity occurred in 48% of patients. Median survival was 15 months, with a survival rate of 38% at 2 years. This substantial survival rate at 2 years reflects that, although all patients were symptomatic before surgery, only half had stage IV disease. Patients with linitis plastica present a very difficult therapeutic challenge. Resection may provide palliation of symptoms; however, survival after total gastrectomy is exceedingly poor, ranging from 3 months to 1 year.

Bozzetti et al.[429,430] have reviewed the outcomes of 246 patients with advanced gastric cancer who underwent simple exploratory laparotomy alone, gastrointestinal bypass, or palliative resection at the National Cancer Institute of Milan. When survival was compared in patients with similar type and extent of disease, a consistent trend was seen for improved median OS with palliative resection in patients with local spread (4 months versus 8 months) and distant spread of disease (3 months versus 8 months). Boddie et al.[431] have reported similar results in 45 patients undergoing palliative resection at the MD Anderson Cancer Center for advanced gastric cancer. Operative mortality for resection was 22%. In 21 patients who had undergone a palliative bypass procedure, OS was significantly shorter than for those undergoing palliative gastric resection ($p < 0.01$).

In select patients with symptomatic advanced gastric cancer, resection of the primary disease appears to provide symptomatic relief with acceptable morbidity and mortality, even in the presence of macroscopic residual disease.

RADIATION FOR PALLIATION

To date, no studies have evaluated the use of radiation therapy in patients with locally recurrent or metastatic carcinoma of the stomach. Its use is likely to be limited to palliation of symptoms such as bleeding or controlling pain secondary to local tumor infiltration. Although minimal data are available, radiation therapy seems to be anecdotally effective in controlling bleeding, as is true in other primary tumor sites. Pain from local tumor invasion can also be palliated with radiation. On rare occasions, a case may arise of a patient with a focal local recurrence without metastases who would be amenable to relatively high-dose radiation therapy in order to try to prolong quality-adjusted survival or in whom radiation therapy would be given as an adjuvant to surgical resection. At present, however, no data support such an approach.

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